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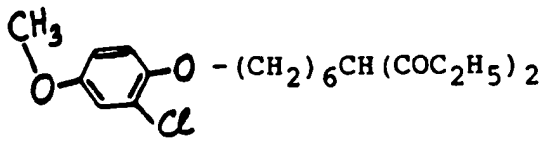
JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 6, June 1985, pag s 747-752, The American Chemical Society, Washington, US ; G.D. DIANA et al.: "Isoxaz l s with An-tipicornavirus Axtivity"	

D scription

This invention relates to compounds with pharmaceutical activity, i.e. antiviral, antiinflammatory and platelet activating factor inhibition, their pharmaceutically acceptable salts and solvates and pharmaceutical compositions containing the active compounds.

Arildone, a compound represented by the formula



is active in vitro against herpes virus and polio virus, but is only marginally active against rhinoviruses. Diana et al., J. Med. Chem. 28, 748 (1985) prepared some alkyl-substituted isoxazole analogs of arildone in an attempt to prepare compounds with broad spectrum activity against picornaviruses. Some of the compounds were active against both rhinovirus type 2 and poliovirus type 2. However, there is no indication that any of the Diana et al. compounds have activity as antiinflammatories or as platelet activating factor inhibitors. Many of the compounds of this invention possess such activity.

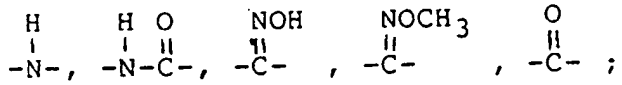
The compounds of this invention are represented by the following structural formula I

Z-X-Q-Y-W I

pharmaceutically acceptable acid addition, basic addition, and quaternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein

each Z is independently tertiary butyl, phenyl, naphthyl or adamantanyl; substituted phenyl, wherein the substituents are one or more of halogen, lower alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl, loweralkylsulfonyl, oxazol-2-yl, lower alkanoyl, benzoyl, lower alkoxycarbonyl, lower alkyl, phenyl, lower alkylthio, phenylaminothiocarbonyl, or lower alkylaminothiocarbonyl; 4 to 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen in the ring with the remaining members of the ring being at least one carbon, and optionally sulfur or oxygen wherein the substituents are one or more of -COOH, $-CH_2OH$, lower alkyl, loweralkylcarbonyl, or aryl lower alkyl;

X and Y are each independently a bond, -O-, -S-, $-SO_2-$,



each Q is independently a divalent substituted or unsubstituted, straight or branched chain, loweralkanediyl-cycloalkanediyl-loweralkanediyl, lower alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tetrahydropyrandiyl, loweralkanediyl-tetrahydrofurandiyl-loweralkanediyl wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;

W is a monovalent substituted or unsubstituted aryl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, lower alkyl, loweralkoxycarbonyl, halogen, sulfamyl, loweralkoxycarbonylloweralkyl, loweralkythio, lower alkoxy, hydroxy loweralkyl, amino loweralkyl, carboxy loweralkyl, guanidino, thioureido, lower alkyl sulfonylamino, aminocarbonylloweralkyl, allyloxycarbonylmethyl or carbamoyloxyloweralkyl, with the proviso that W cannot be substituted or unsubstituted isoxazolyl.

Compounds of formula II with structure Z-X-Q-Y-W'-Y-Q-X-Z in which W' is divalent W form the subject of a separate invention.

The invention also includes pharmaceutical compositions containing pharmaceutically effective amounts of a compound of formula I or formula II as well as method of treating virus infections, inflammation and inhibiting platelet activating factor using the appropriate pharmaceutical compositions.

As used herein "lower alkyl" alone or in combined form, e.g. "lower alkoxy" or "loweralkanediyl", means straight or branched chain alkyl groups of from 1 to 10 carbon atoms, e.g. methyl, ethyl, propyl,

isopropyl, butyl, t-butyl, pentyl, neopentyl, hexyl and the like.

The heterocyclics at Z and W are monovalently bonded to X and Y respectively by a hetero atom, preferably nitrogen, or by a carbon atom. The heterocyclics at W' preferably have two nitrogens, each of which is bonded to a separate -Y-Q-X-Z moiety.

Heterocyclic groups within the scope of this invention for Z are, for example, imidazolyl (such as imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, and imidazol-5-yl), dihydrothiazolyl (such as 4, 5-dihydrothiazol-2-yl), tetrazol (such as tetrazol-5-yl, tetrazol-1-yl, and tetrazol-2-yl), pyridinyl (such as pyridin-2-yl), triazolyl (such as 1, 2, 4-triazol-1-yl), tetrahydro-pyrimidinyl (such as 1, 2, 3, 4-tetrahydro-pyrimidin-1-yl), dihydro-oxazolyl (such as 4, 5-dihydro-oxazol-2-yl), pyrrolidinyl (such as pyrrolidin-1-yl), pyrazolyl (such as pyrazol-1-yl and pyrazol-2-yl), morpholinyl, and azetidinyl. All possible attachment positions of the above heterocyclic groups are within the scope of this invention.

Heterocyclic groups within the scope of this invention for W are, for example, all those listed above for Z and, in addition, fused ring compounds, for example benzamidazolyl (such as benzamidaol-1-yl and benzamidazol-2-yl), naphthyridinyl (such as naphthyridin-l-yl), purine (such as purine-9-yl and purine-7-yl), and quinolinyl.

Heterocyclic groups within the scope of this invention for W' are all those listed above for Z and W, but being divalent. For example, if W' were tetrahydro-pyrimidinyl, it could be 1, 2, 3, 4-tetrahydro-pyrimidin-1, 3-diyl. W' as a bernzamidazolyl group could be, for example benzamidazol-1,3diyl. In other words, to obtain a possible W' group from the groups listed for Z and W, the "yl" suffix in the Z and W radical is replaced by "diyl".

"Aryl" as used herein refers to phenyl and naphthyl.

"Halogen" as used herein means chlorine, fluorine, bromine or iodine with chlorine or fluorine preferred.

"Cycloalkane", alone or in combined form, means a 4, 5, 6 or 7 membered saturated carbocylic ring.

"Lower alkene", alone or in combined form, means a 2 to 10 carbon branched or straight chain alkene group.

"Lower alkyne", alone or in combined form, means a 2-10 carbon branched or straight chain alkyne group.

"Pharmaceutically acceptable salts" as used herein means acid addition salts formed from mineral acids such as hydrochloric, hydrobromic, phosphoric or sulfuric acids, or formed from organic carboxylic or sulfonic acids such as trifluoracetic, para-toluene, sulfonic, maleic, acetic, citric, oxalic, succinic, benzoic, tartaric, fumaric, mandelic, ascorbic and malic acids, or quaternary salts prepared from such organic halides as methyl iodide, ethyl idodide, benzyl chloride and the like, although all pharmaceutically acceptable quaternary salts are contemplated. Basic addition salts are also within the scope of this invention.

The above salts are made by conventional means in the art, e.g. reaction of the compound with the appropriate acid, organic halide, or base.

The preferred salt is the hydrochloride salt.

"Hydroxy protecting group" as used herein means any known hydroxy protecting group which is removed by conventional reactions which do not adversely affect the compounds produced. Typical suitable hydroxy protecting groups are t-butyldimethysilyl (TBDMS) or tetrahydro-pyranyl.

The compounds of this invention have been found to be active against ether-resistant RNA viruses, i.e. picornaviruses which includes enteroviruses and rhinoviruses. The enteroviruses include poliovirus, coxsackieviruses and echoviruses. Rhinoviruses include those viruses associated with the common cold and certain other respiratory ailments. Over one hundred serotypes are identified. Although the compounds of this invention are not active against all the rhinoviruses, they are active against a large number of them including rhinovirus 2. The compounds of this invention are also active against the enteroviruses such as poliovirus 2, coxsackieviruses A and B3, ECHO and hepatitis A.

In addition, the compounds of this invention are active against certain DNA viruses such as herpesvirus and cytomegalovirus. Thus, they showed activity when tested in vitro activity assays, i.e. plaque reduction assays which measure the ability of synthetic cojpounds to neutralize virus infectivity, e.g. picornavirus infectivity. In tests against coxsackievirus 3, the IC_{50} values of the tested compounds of this invention varied from about 0.7 microgram/ml to about 1.4 microgram/ml. The IC_{50} value in all antiviral tests is the concentration of test compound in micrograms per milliliter which results in a 50% decrease in plaque forming units compared to a non-treated control.

In a modified standard test, i.e. wherein the virus and test compound are mixed and incubated prior to overlaying with an agar medium active compounds of this invention had IC_{50}s of from about 6.0 to about 37.3 against poliovirus 2, about 8.5 to about 39.5 against human rhinovirus 14 and about 2.4 to 5.0 against cosackievirus B3.

The standard test involves overlaying HeLa cells with agar medium containing measured concentrations of the test compound following virus absorption, then incubating for 72 hours. The resulting plaques are stained, visualized and measured to determine virus growth inhibition as evidenced by plaque reduction when compared to a control.

The modified standard test is considered more sensitive because of its ability to discriminate more clearly the virus growth neutralizing effects between compounds whose IC_{50}s are very close according to the standard test.

Of the antiviral compounds within the scope of formulas I and II, those which form water soluble acid addition salts are orally absorbable, show good tissue levels and serum stability.

The preferred antiviral compounds of this invention are those represented by the following formula III

Z^1-X^1-Q^1-W^1 III

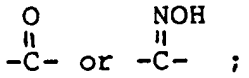
and pharmaceutically acceptable acid addition salts thereof,

wherein

Q^1 is lower alkynediyl of 6, 7 or 8 carbon atoms; and all possible isomers of methylcyclohexylmethyl,

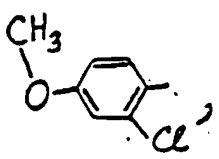
W^1 is unsubstituted or substituted imidazo-1-yl, purin-9-yl or imidazo-2-yl, wherein said substituents are one or more of loweralkyl, hydroxy loweralkyl, nitro, lower alkoxycarbonyl, carboxymethyl, aminocarbonylmethyl;

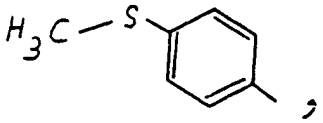
X^1 is -O-,



and

Z^1 is





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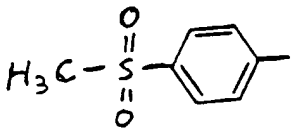


The preferred acid addition salt is the hydrochloride.

Certain compounds of this invention have been found to display activity in animal models of inflammation, Thus, in a reverse passive Arthus reaction in rats, the compounds were orally active when administered at dosages of from 25 to 100 mg/kg and in the adjuvant induced arthritis test in rats were orally active.

The reverse passive Arthus test evaluates test compounds for activity against an immune complex, cell-mediated inflammatory reaction. In the performance of the test, rats previously fasted for 24 hours are dosed with the test compound, then after one hour are lightly anesthesized and injected (iv) with 1.0 mg bovine serum albumin (BSA) in 0.1 ml sterile saline. Then the rats are injected intrapleurally with 0.1 ml sterile saline containing 100 micrograms of antibody protein to bovine serum albumin.

Four hours after challenge, the rats are sacrificed and pleural cavity transudate is removed and the volume recorded. The pleural cavity is then washed with 3 ml of cold saline and the wash is removed and added to the original transudate. After being treated with an anticlot agent or EDTA, the transudate is cooled on ice and the volumes of the test transudate and control transudate are adjusted to 5.5 ml with saline and their white blood cell counts are determined on a Z1 Coulter Counter. The differences between transudate

volume (a measure of edema) and total white blood cell counts (a measure of neutrophil accumulation) between the controls and drug treated groups is a measure of the drugs antiinflammatory activity. These effects are stated as a percent inhibition or reduction in neutrophil count and transudate volume.

The adjuvant induced arthritis test in rats evaluates the effect of a drug on an immune mediated model of chronic inflammation. In the performance of the test, animals (rats) are dosed orally with drugs at a volume of 1 ml per 100 grams of body weight. The drug concentration is varied for different test dosages. The rats are dosed with the test compound one hour prior to sensitization with an adjuvant. The adjuvant used in this test model is heat killed mixed M. tuberculosis homogenized in paraffin oil. Controls are given the methylcellulose vehicle alone.

The adjuvant is injected into the subplantar region of the left hind paw, immediately thereafter the volumes of the left and right hind paws are measured with a plethysmograph. Injected paw volumes are measured after 24 hours and then 21 days later. The contralateral hind paw is only measured 21 days later. The differences in paw volumes between the first and last measurements are related to the degree of inflammation. Antiinflammatory drugs reduce these differences.

The compounds of this invention which exhibit antiinflammatory activity are those with an imidazo-1-yl or lower alkyl substituted imidazo-1-yl at the W position of formula I.

Certain of the compounds of this invention have been found to display platelet-activating factor (PAF) antagonism. PAF has been shown to be involved in the pathophysiology of various allergic and inflammatory diseases. It is an important mediator of such processes as platelet aggregation, smooth muscle contraction, especially lung tissue, vascular permeability and neutrophil activation. Furthermore, recent evidence implicates PAF as the underlying factor involved in airway hyperreactivity. As such, PAF is implicated in diseases such as asthma (bronchoconstriction and pulmonary edema) and inflammation.

Antagonists or inhibitors of PAF, such as the compounds of this invention, would therefore be of use whenever PAF is a factor in the disease or disorder. This includes allergic diseases such as asthma, adult respiratory distress syndrome and urticaria, and inflammatory diseases such as rheumatoid arthritis and osteoarthritis.

In the in vivo PAF Induced Bronchiospasm in Guinea Pigs, compounds of this invention exhibit IC_{50} values of from about 3 to about 60 mg per kg. In the in vitro PAF Antagonism Assay, compounds of this invention show an inhibition of PAF activity from about 20 to 100% at varying concentrations.

The PAF Induced Bronchiospasm in Guinea Pigs assay is conducted as follows:

Non-sensitized guinea pigs were fasted overnight, and the following morning were anesthetized with 0.9 ml/kg i.p. of dialurethane (0.1 gm/ml of diallylbarbituric acid, 0.4 gm/ml of ethylurea and 0.4 gm/ml of methane). The trachea was cannulated and the animals were ventilated by a Harvard rodent respirator at 55 strokes/min with a stroke volume of 4 ml. A side arm to the tracheal cannula was connected to a Harvard pressure transducer to obtain a continuous measure of intratracheal pressure, which was measured on a Harvard polygraph. The jugular vein was cannulated for the administration of compounds. The animals were challenged i.v. with PAF (0.4 µg/kg in isotonic saline containing 0.25% BSA) and the peak increase in inflation pressure that occurred within 5 min. after challenge was recorded. Test compounds were administered either orally (2 hours prior to PAF as a suspension in 0.4% methyl cellulose vehicle) or intravenously (10 minutes prior to PAF as a solution in DMSO).

The effect of compounds on the bronchoispasm is expressed as a percent inhibition of the peak increase in intratracheal pressure compared to the peak increase in the control group. The IC_{50} is the dosage in mg/kg required to obtain a 50% inhibition.

The in vitro PAF Antagonism Assay as conducted as follows:

Platelet-activating factor (PAF) causes aggregation of platelets in a receptor-mediated mechanism. Therefore, PAF-inducced platelet aggregation provides a simple and convenient assay to screen compounds for PAF antagonism.

Preparation of platelet-rich plasma (PRP)

Human blood (50 ml) is collected from healthy male donors in an anticoagulant solution (5 ml) containing sodium citrate (3.8%) and dextrose (2%). Blood is centrifuged at 110 X g for 15 min. and the supernatant (PRP) carefully transferred into a polypropylene tube. Platelet-poor-plasma (PPP) is prepared by centrifuging PRP at 12,000 X g for 2 min. (Beckman Microfuge B). PRP is used within 3 hours of drawing the blood.

Platelet Aggregation Assay

When an aggregating agent such as PAF is added to PRP, platelets aggregate. An aggregometer quantifies this aggregation by measuring and comparing light (infra-red) transmission through PPP and PRP. The aggregation assays performed on the compounds of this invention are performed using a dual-channel aggregometer (Model 440, Chrono-Log Corp., Havertown, PA). PRP (0.45 ml) in aggregometer curettes is continually stirred (37 °C). Solutions of test compounds or vehicle are added to the PRP, and after incubation for 2 min., 10-15 µl aliquots of PAF solution are added to achieve a final concentration of 1-5 X 10^{-8} M. Incubations are continued until the increase in light transmission reaches a maximum (usually 2 min.). Values for inhibition are calculated by comparing maximal aggregation obtained in the absence and the presence of the test compound and expresed as percent inhibition. For each experiment, a standard PAF antagonist such as alprazolam is used as a positive internal control.

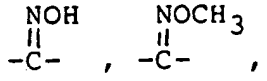
Preferred PAF antagonist compounds of this invention are represented by the following formula V:

Z^2-X^2-Q^2-Y^2-W^2 V

pharmaceutically acceptable acid addition salts or quaternary amine salts thereof, wherein

Z^2 is phenyl; substituted phenyl wherein the substituents are independently one or more of halogen, loweralkylthio, loweralkylsulfonyl, lower alkoxy, oxazol-2-yl, phenoxy; imidazol-1-yl; lower alkyl substituted imidazol-1-yl; or tert-butyl;

X^2 is a bond, -O-,



-S-,

or $-SO_2-$;

Q^2 is lower alkanediyl of 5, 6 or 7 carbon atoms optionally substituted by -OH; loweralkynediyl of 6-8 carbon atoms; or methylcyclohexylmethyl;

Y^2 is a bond, -S- or $-SO_2-$; and

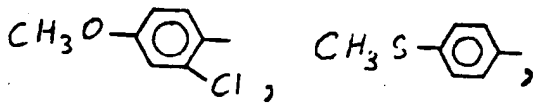
W^2 is imidazol-1-yl; substituted imidazol-1-yl wherein the substituents are independently one or more of loweralkyl, hydroxy loweralkyl, aminoloweralkyl and lower alkoxycarbonyl; imidazol-2-yl; imidazol-4-yl; imidazol-5-yl; substituted imidazol-2-yl, -4-yl or -5-yl, wherein the substituents are independently one or more of lower alkyl, and allyloxycarbonylmethyl; pyrrolidin-1-yl; benzimidazol-1-yl; 1,4 dihydro-4-oxo-7-methyl-1,8-3-carboxyl-naphthyridin-1-yl; purin-9-yl; pyridin-2-yl; pyrazol-1-yl; or benzimidazol-2-yl.

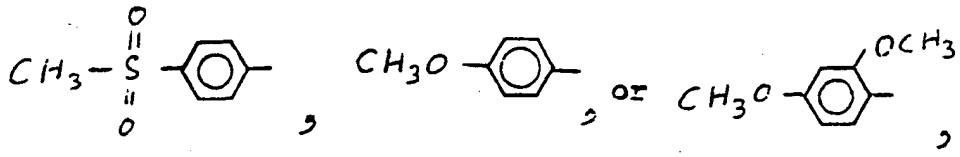
The most preferred compounds having PAF activity are represented by the following formula VI

Z^3-X^3-Q^3-W^3

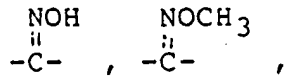
and pharmaceutically acceptable acid addition or quaternary salts thereof, wherein

Z^3 is



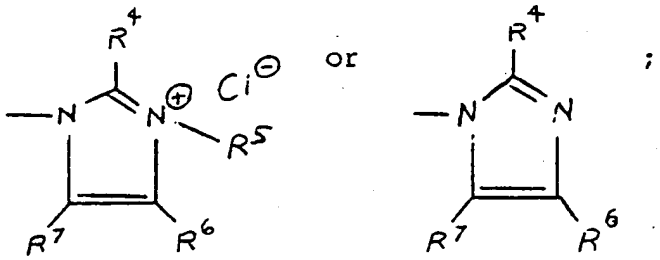


X^3 is



-S-, -O-, or

Q^3 is lower alkanediyl of 5, 6 or 7 carbon atoms optionally substituted by -OH;
W^3 is



and
R^4 is hydrogen, loweralkyl or hydroxy loweralkyl;
R^5 is lower alkyl;
R^6 and R^7 are independently one or more of hydrogen, loweralkyl, amino loweralkyl or nitro.

The compounds of this invention are conventionally formulated for oral, parenteral, topical and transdermal use, oral is preferred.

This invention includes within its scope pharmaceutical compositions comprising the compounds of this invention in admixture with a pharmaceutically acceptable carrier therefor. In addition, the present invention also includes the use of the compounds of formula I for preparing pharmaceutical compositions useful for treating viral infections or inflammation, or for inhibiting platelet activating factor. In the foregoing compositions, the active compounds of this invention can be used alone as the sole active antiviral agent, sole active antiinflammatory agent or sole active PAF antagonist, or in combination with other therapeutic agents.

For the preferred oral administration, the compounds of this invention are typically formulated in the form of tablets, capsules, elixirs, solutions, suspensions and the like preferably solutions. For parenteral administration, they may be formulated into solutions or suspensions. Topical formulations such as lotions, creams ointments sprays and mechanical delivery devices, e.g. transdermal can also be made with the compounds of this invention.

Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars such as lactose, startches such as corn starch, cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; and other carriers well known in the art. The

compositions may also contain preservatives, aerosol propellants and coloring, thickening, suspending, dispensing, emulsifying, wetting, stabilizing and buffering agents.

The dosage of the compounds of this invention which is administered is dependent, in the judgment of the attending clinician, upon a variety of factors, e.g. the age and weight of the individual being treated, the mode of administration, the potency of the administered compound, the indication for which the drug is administered and the severity of the ailment being treated.

Typically, the dosage administered per day for treating viral infections will be oral administration of from about 1 mg/kg to about 75 mg/kg daily in single or divided doses, with about 1-25 mg/kg preferred. The dosage for treating inflammation is about 25 mg to about 2 gm administered daily in divided doses, with the preferred range being about 25 to about 100 mg.

In order to achieve PAF antagonism, oral administration daily in single or divided doses of about 2.5 mg/kg to about 50 mg/kg can be used, preferably about 2.5 mg/kg to about 25 mg/kg. Intravenous administration can be about 0.5 mg/kg to about 10 mg/kg per day with 0.5 mg/kg to about 5 mg/kg preferred.

The compounds of this invention are prepared by the following methods:

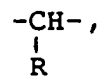
(A) to produce a compound of formula I, reacting a compound of the formula

$Z\text{-}X\text{-}Q'\text{-}L^1$

wherein Z and X are as defined previously,

Q' is the same as Q defined previously, or, provided Q in formula I is to contain at least one of the group

wherein each R is independently hydrogen or lower alkyl, Q' may also be the same as Q defined above minus at least one of the groups



and

L^1 is a leaving group, with a compound having the formula

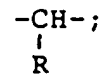
$L^2\text{-}Y'\text{-}W''$

where L^2 is a leaving group,

W'' is as defined for W in formula I, or a tautomer thereof, and

Y' is the same Y defined in formula I, or, provided Q in formula I is to contain at least one of the groups

wherein each R is independently hydrogen or lower alkyl, Y' may also be the same as Y defined in formula I plus at least one of the groups



or

(B) to produce a compound of formula I, at least one compound of the formula

$Z\text{-}X\text{-}Q'\text{-}L^1$

wherein Z, X, Q' and L^1 are as defined previously is reacted with a compound of the formula

$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$

wherein L^3 and L^4 are leaving groups
each Y' is independently as defined above, and
W''' is divalent W' as defined above, or
(C) to produce a compound of formula I wherein Z and W are the same and X and Y are the same, reacting a compound of the formula

$L^2\text{-}Y'\text{-}W''$

wherein Y' and W'' are as defined previously and
L^2 is a leaving group, with a compound of the formula

$L^5\text{-}Q''\text{-}L^6$

wherein L^5 and L^6 are leaving groups and Q'' is divalent Q' as defined above,
wherein in the above processes, any reactive groups are protected if necessary or desired,
the above processes followed, if necessary or desired. by
(i) removal of any protecting groups,
(ii) conversion of a compound so produced to another compound of formula I,
(iii) if more than one compound of formula I is produced, separation of the compounds so produced, or
(iv) conversion of any of the compounds so produced to an acid addition, basic addition, or quaternary amine salt or pharmaceutically acceptable solvate thereof.

In process (A), L^1 is preferably bromine or most preferably iodine and L^2 is a preferably alkali metal such as sodium, potassium or cesium. The reaction takes place at temperatures of from about -20 °C to 60 °C in an inert organic solvent such as dimethylsulfoxide (DMSO), dimethylformamide (DMF) or tetrahydrofuran (THF). In most cases the final compounds can be converted to water-soluble acid addition or quaternary salts by conventional reactions, e.g., with hydrochloric acid or a quaternizing agent such as methyl sulfonic acid.

The starting compounds $Z\text{-}X\text{-}Q'\text{-}L^1$ wherein L^1 is halogen (Hal) are prepared by the following reaction:

$$ZXH + Hal\text{-}Q'\text{-}Hal \xrightarrow[\text{acid scavenger}]{} Z\text{-}X\text{-}Q\text{-}Hal$$

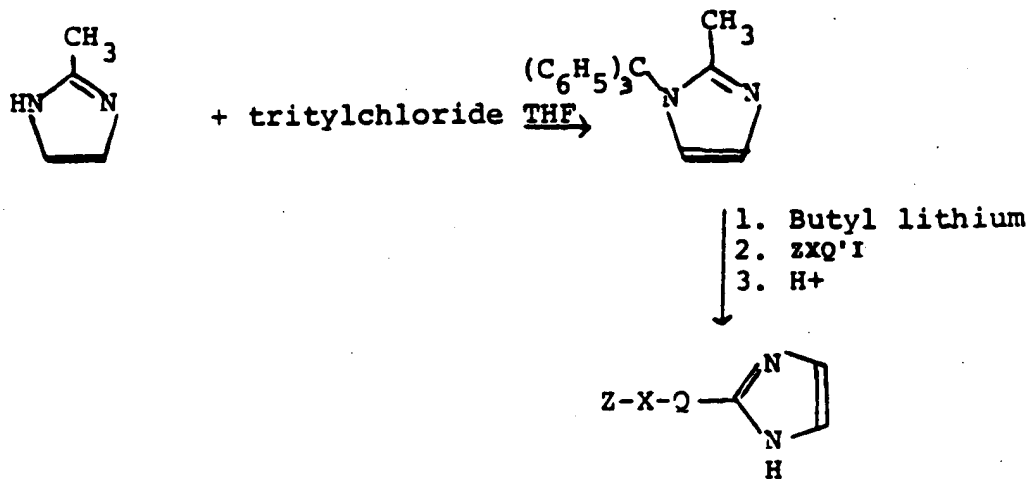
wherein Z, X and Q' are as defined above.

The reaction takes place in the presence of an acid scavenger such as K_2CO_3 or organic bases such as collidine and also Hunigs base. The preferred Hal group is iodine although bromine can also be used. The compound Hal-Q'-Hal wherein Hal is iodine can be prepared by reacting Br-Q'-Br with sodium iodide except when Q is $-CH_2-$ or $-CH_2-CH_2-$.

Alternatively ZXQ'-I can be prepared by reacting ZXH with Br-Q'-Br to obtain ZXQ'Br, then reacting ZXQ'Br with sodium iodide to obtain Z-X-Q'-I. Or for compounds when Q' is $-CH_2-$ or $-C_2H_4-$, Z-X-Q'-I can be prepared by reacting the corresponding mono or dihydric alcohol with HI.

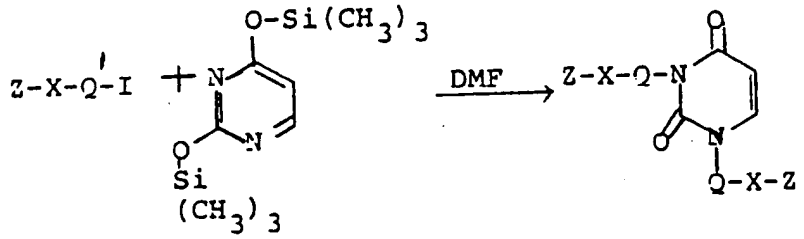
When W is a nitrogen containing heterocyclic moiety, the processes described above result in the W moiety being substituted at a nitrogen atom of the heterocyclic ring, unless the nitrogen atom is protected. In order to make a compound wherein the heterocyclic is substituted at a ring carbon, it is necessary to protect the nitrogen with a group which is easily removed after the C-substitution is carried out and is not removed during the C-substitution reaction, e.g., the trityl group.

Thus, for example, in the preparation of a 2-substituted imidazole, the following reaction scheme is followed:



wherein Q, Q', Z and X are as defined above. In this case the methyl group on the imidazo ring becomes part of Q in the compound produced.

In process (B) to make a compound of formula II, the W' moiety should have two ring carbons initially substituted with trimethylsilyloxy groups. When the reaction with Z-X-Q'-I is conducted, the resulting product is a disubstituted W' moiety as shown in the following reaction in which the trimethylsilyloxy substituted compound is illustrated as a pyrimidine.

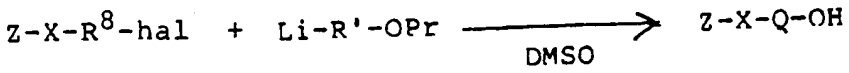


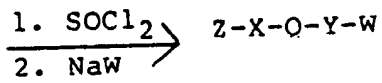
The reaction is carried out at room temperature.

In process (B) if an excess of the compound Z-X-Q'-L^1 is used, the product will primarily be of formula II. However, if only small amounts of the compound Z-X-Q'-L^1 is used, products of formulas I and II will be produced. The reaction conditions are the same as in process (A).

Process C, which produces compounds of formula I wherein Z and W are the same and X and Y are the same, is carried out under the same reaction conditions as process (A).

The preparation of compounds wherein Q is an unsaturated chain, i.e. an alkynediyl is illustrated in the following reaction:

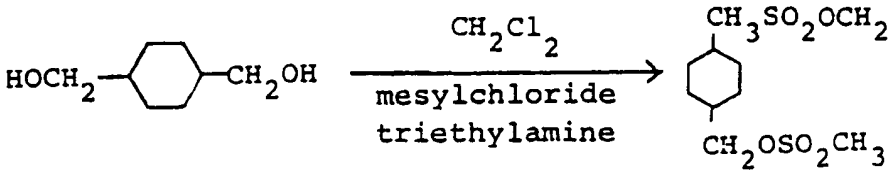


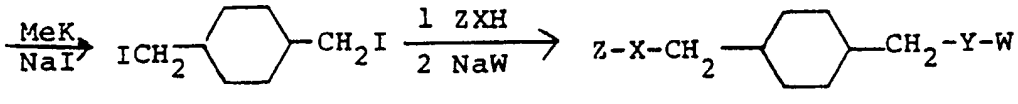


I

wherein R^8 is lower alkyl of 2 to 4 carbons and R' is lower alkynyl of 3 carbons, Y is a bond, Pr is a hydroxy protecting group and hal is bromine or iodine.

The preparation of compounds in which Q is an alkyl having a cycloalkane in the chain is illustrated by the following reaction:





wherein hal is bromine or iodine and Z, X, Y and W are as defined above for formula I.

A compound of formula I or II can be converted to a different compound of formula I or II, respectively, by standard techniques well known in the art. Such conversion techniques are illustrated in the examples.

In general preparing the compounds of this invention involves relatively simple procedures as illustrated by the many Examples which appear later in this text.

The following Table I shows compounds of formula I prepared by the processes described above and in Examples 1 -4.

Table II shows compounds, related to those of formula I, prepared by the processes described in Examples 5-21.

Table III shows additional compounds of formula I which can be prepared by following the procedures of the Examples which follow by substituting the appropriate starting materials.

Table I

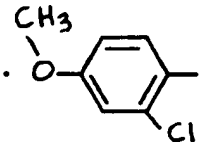
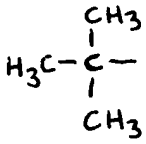
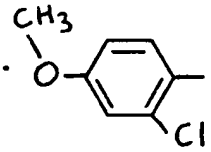
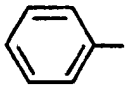
Example	Z	X	Q	Y	W	Salt
1.		-O-		bond		HCL
2.		bond	$-C\equiv C-(CH_2)_6-$	"	"	"
3.		-O-	$-(CH_2)_3-C\equiv C-CH_2-$	"	"	"
4.		bond	$-C\equiv C-(CH_2)_6-$	"	"	"

TABLE II

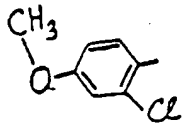
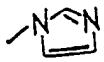
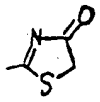
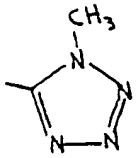
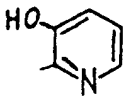
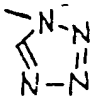
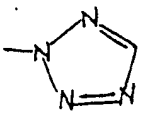
Example	Z	X	Q	Y	W	Salt
5.		-O-	$-(CH_2)_6-$	bond		HCl
6.	"	"	"	-S-		—
7.	"	"	"	"		—
8.	"	"	"	-S-		—
9.	"	"	"	bond		—
9A.	"	"	"	"		—

Table II (contd)

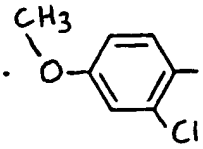
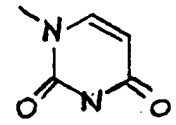
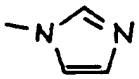
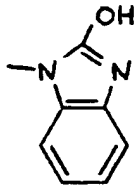
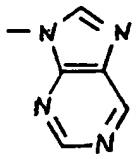
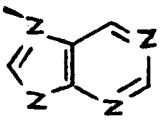
Example	Z	X	Q	Y	W	Salt
10.		-O-	$-(CH_2)_6-$	bond		-
11.	"	-O-	$-(CH_2)_5-$	"		HCl
12.	"	-O-	$-(CH_2)_6-$	"		-
13.	"	-O-	"	"		-
13A.	"	"	"	"		"

Table II (contd)

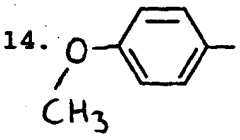
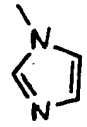
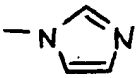
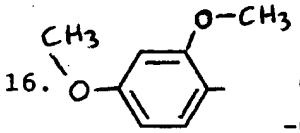
Example	Z	X	Q	Y	W	Salt
14. 		$-\overset{O}{\overset{\|\|}{C}}-$	$-(CH_2)_6-$	bond		HCl
15.	"	$-\overset{NOH}{\overset{\|\|}{C}}-$	"	"		"
16. 		$-\overset{O}{\overset{\|\|}{C}}-$	$-(CH_2)_5-$	"	"	"
17.	"	$-\overset{OH}{\overset{\|}{C}}-$	"	"	"	-
18.	"	bond	$-CH=CH(CH_2)_4-$	"	"	HCl

Table II (contd)

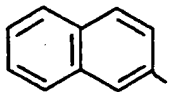
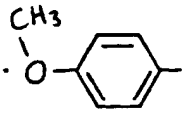
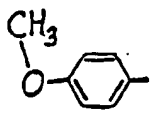
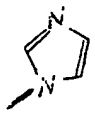
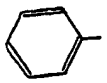
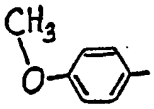
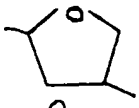
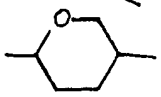
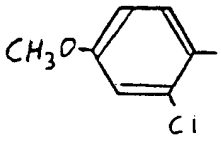
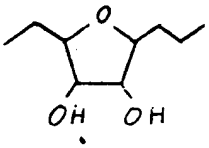
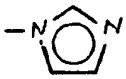
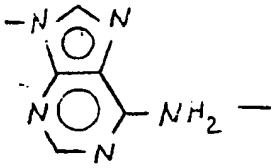
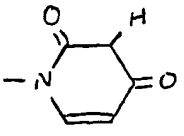
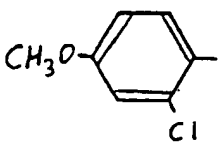
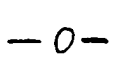
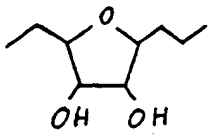
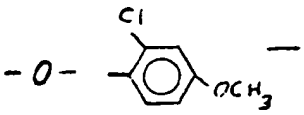
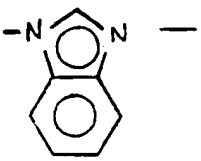
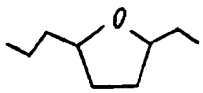
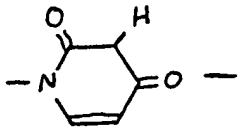
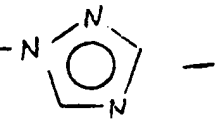
Example	Z	X	Q	Y	W	Salt
19.		-O-	$-(CH_2)_6-$	bond		HCl
20.		-S-	$-(CH_2)_6-$	bond	"	"
21.	"	$-SO_2-$	"	"	"	"

Table III

Z	X	Q	Y	W	Salt
		$-(CH_2)_6-$	bond		HCl
	bond	$-(CH_2)_6-C\equiv C-$	"	"	"
	"	$-(CH_2)_6-C\equiv C-$	"	"	"
"	"		"	"	"
"	"		"	"	"
"	"		"	"	"
	— O —		"		—
"	"	"	"		—
"	"	"	"		—

Z	X	Q	Y	W	Salt
					
〃	〃	〃	bond		
〃	〃		〃		
〃	〃	〃	〃		
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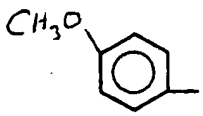
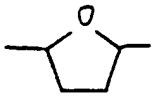
	bond		〃	〃	HCl

The starting materials for use in the preparation of the compounds of this invention are either commercially available or are prepared by conventional means known in the art.

The following examples illustrate the invention. Fast atom bombardment (FAB) mass spectra (MS) were run on a Finnigan MAT 312 double focussing mass spectrometer, operating at an accelerating voltage of 3 kV. The MS samples were ionized by bombardment with xenon atoms produced by a saddle field ion source from Ion Tech operating with a tube current of 2 mA at an energy of 6 KeV. The proton nuclear magnetic resonance (H^1-NMR) spectra were recorded at 200 MHz on a Varian XL-200 spectronometer; all chemical shift values δ are reported in ppm downfield from tetramethylsilane.

EXAMPLE 1

Trans 1-[(2-chloro-4-methoxyphenoxy)methyl]4-[(1-imidazolyl)methyl]cyclohexane

(a) Add 14.5 gm. of trans 1,4-bis hydroxymethyl cyclohexane to 250 ml. methylene chloride and add 20 ml. methanesulfonyl chloride, cool to 0 °C and slowly add 36 ml. triethylamine over a period of one hour.

Remove the solvent, extract with water, filter and wash with methanol to obtain trans 1,4-bis mesylate methyl cyclohexane.

(b) Add 30 gms. of the mesylate prepared in step (a) to 300 ml. methylethyl ketone (MEK), then add 90 gm. sodium iodide and reflux for about 30 minutes. Remove the solvent and extract with methylene chloride to yield trans 1,4-bis iodomethyl cyclohexane.

(c) Add 3 gms. of 2-chloro-4-methoxyphenol, 15 gms. of the diodo compound prepared in step (b), 100 ml. water, 100 ml. methylene chloride in a reaction flask, add 0.5 gm (n-butyl) ammonium sulfate and 25 ml 50% aqeuous NaOH. Elute on a silica column. A mixture of mono and bis ether results as evidenced by NMR.

Add the resulting mixture to 3 gm. sodium imidazole in 20 ml. DMF. Stir at room temperature for about 48 hours. Remove the solvent and elute on a silica column with 100% methylene chloride then 5% methanol to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

FAB-MS: m/z 335 (M^+) HCl salt, H^1-NMR-200 mHz, $^\delta$H ($CDCl_3$), 0.9-1.30 (4H,m), 1.6-2.1 (6H,m), 3.75 (3H,s), 3.77 (2H,d,J 6Hz), 4.2 (2H,d,J 6Hz), 6.7-7.0 (3H,m), 7.14 (1H,s), 7.43 (1H,s), 9.55 (1H,s).

EXAMPLE 2

1-(9,9-dimethyl-dec-7-ynyl)-imidazole

(a) Add 5 ml. freshly distilled THF and 413 mg. 3,3-dimethyl-1-butyne to a dry reaction flask, cool to -78°C then add 2.01 ml. n-butyl lithium (2.5M in hexane), stir about 30 minutes at -78°C, transfer into 3 ml. THF and 4.9 gm. 1,6-dibromo hexane at 0°C, stir 6 hours and add 2 ml. dry DMSO to form a precipitate. Wash with water, in methylene chloride. Elute through a short bed of silica with hexane to remove polar material giving a mixture of 1,6-dibromo hexane and 1 bromo-(9,9-dimethyl-dec-7-yne.

(b) Stir overnight at room temperature 4.73 gm. of the mixture prepared in step (a), 5 ml. DMF and 2.1 gm. sodium imidazole, in a reaction flask. Add methylene chloride, wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride, then 2% methanol/methylene chloride. Combine fractions containing product and chromatograph on a coarse silica column with 25% ethylacetate/methylene chloride, then 35% ethylacetate/methylene chloride to isolate the title compound.

Prepare the hydrochloride salt by reaction with about 1.1 eq. of 0.1N HCl.

EXAMPLE 3

1-[6-(2-chloro-4-methoxyphenoxy)-hex-2-ynyl]imidazole

(a) Add 30 ml. THF and 10 ml. DMSO to a reaction flask and cool to -78°C. Add 7.4 ml. n-butyl lithium (2.5M/hexane), stir for five minutes and add 2.6 gms. of tetrahydropyran protected propargyl alcohol and warm to room temperature. Stir 5 minutes and add 3 gms. of 1-(2-chloro-4-methoxyphenoxy)propyl-3-bromide resulting in a slightly exothermic reaction. Stir for about 1.5 hours. Remove the THF by vacuum and partition with water/methylene chloride. Elute the methylene chloride residue on a silica column with 25% methylene chloride/hexane then 50/50 methylene chloride/hexane. Add the resulting product to 50/25/25 THF/H_2O/CH_3OH and add 1 gm. para toluene sulfonic acid. Stir overnight, remove THF/methanol, partition with 5% $NaHCO_3$/CH_2Cl_2 then with water/methylene chloride. Remove the CH_2Cl_2 to obtain the desired product, 1-hydroxy-6-(2-chloro-4-methoxyphenoxy)hex-2-yne.

(b) Add 25 ml. thionyl chloride to 1.17 gms. of the compound prepared in step (a) and reflux for 1 hour. Remove the thionyl chloride. Add 25 ml. DMF and 3 gms. sodium imidazole and stir overnight. Remove the DMF and partition with H_2O/CH_2Cl_2.

Elute on a silica column with 100% CH_2Cl_2 then 100% ethylacetate to obtain the title compound.

Prepare the hydrochloride salt by reaction with about 1 eq. of 0.1N HCl.

FAB-MS: m/z 305 HCl salt, H^1-NMR, 200 mHz, $^\delta$H($CDCl_2$), 2.05 (2H,m), 2.55 (2H,m), 3.78 (3H,s), 4.08 (2H,t,J 5Kz), 5.20 (2H,m), 6.7-7.0 (3H,m), 7.30 (1H,s), 7.38 (1H,s), 9.6 (1H,s).

EXAMPLE 4

1-(8-phenyl-oct-7-ynyl)imidazole

(a) Prepare 6-phenylethynylhexyl-1-bromide by adding 1.07 ml phenylacetylene to 10 ml of THF in a reaction flask, cool to -78 °C then add 3.9 ml n-BuLi (2.5 molar in hexane), stir 5 minutes, warm to 0 °C and add 45 ml of 1,6-dibromohexane and 5 mol of dry DMSO. Stir at room temperature for 1.5 hours, remove solvent and treat with methylene chloride and water to recover the product.
(b) Stir for 48 hours at room temperature in a reaction flask, 1.65 gms of the product of step (a) and 1.68 gm sodium imidazole in 5 ml DMF. Remover the resulting title compound by treating with methylene chloride, washing with water and drying over sodium sulfate. Then elute on a coarse silica column with 100% methylene chloride followed by 2% CH_3OH/CH_2Cl_2 to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N HCl.
MS: m/z 253 (M^+) HCl salt.

EXAMPLE 5

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]imidazole

Add 200 mg. 6-(2-chloro-4-methoxyphenoxy)hexyl-1-bromide in 1.5 ml of dimethyl formamide (DMF) to 180 mg sodium imidazole in a reaction vial at room temperature, stir 2 hours then add 20 mg sodium iodide, stir overnight. Add methylene chloride, wash with water then brine, elute on a coarse silica column with methylene chloride then a mixture of 50% ethylacetate and methylene chloride (v/v) to isolate the title compound.

EXAMPLE 6

2-{[6-(2-chloro-4-methoxyphenoxy)hexyl]thio} -4,5-dihydrothiazol-4-one

(a) Reflux about 500 mg sodium iodide in 10 ml of acetone with 350 mg. 6-(2-chloro-4-methoxyphenoxy)-hexyl-1-bromide for 5 to 10 minutes, remove the acetone by bubbling nitrogen through the reaction mixture, add methylene chloride, wash with water, then brine and dry over sodium sulfate to obtain 6-(2-chloro-4-methoxyphenoxy)hexyl-1-iodide.
(b) Add 3 grams of 6-(2-chloro-4-methoxyphenoxy)hexyl-1-iodide in 10 ml acetonitrile to 1.2 g rhodanine and 20 g cesium carbonate. Stir overnight, then remove the acetonitrile, add methylene chloride and wash with water then brine and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride followed by 5% ethylacetate/methylene chloride and finally 10% ethylacetate/methylene chloride to yield the title compound isolation.

EXAMPLE 7

5-{[6-(2-chloro-4-methoxyphenoxy) hexyl]thio}-1-methyltetrazole

Reflux 350 mg. 6-(2-chloro-4-methoxyphenoxy) hexyl-1-bromide with 10 ml of acetone and about 500 mg. sodium iodide for five to ten minutes, remove the acetone by bubbling nitrogen through the reaction mixture, add methylene chloride, wash with water, then brine and dry over sodium sulfate to obtain 6-(2-chloro-4-methoxyphenoxy)hexyl-1-iodide. Add 133 mg of 5-mercapto-1-methyltetrazole, 268 mg. cesium carbonate and 3 ml acetonitrile to the iodide product, stir overnight, add methylene chloride and wash with water, sodium carbonate, water, then brine and dry over sodium sulfate. Remove the solvent and recover the title compound as crystals.

EXAMPLE 8

2-{[6-(2-chloro-4-methoxyphenoxy) hexyl]-thio}-3-pyridinol

Stir 300 mg. of the iodide prepared in Examples 2 or 3, 3 ml. acetonitrile 112 mg. 2-mercapto-3-pyridinol and 201 mg. cesium carbonate in a reaction flask overnight at room temperature. Remove the acetonitrile and add methylene chloride. Wash with sodium carbonate solution, water, then brine and dry

over sodium sulfate. Remove the solvent then add methylene chloride, heat to dissolve the mixture, add hexane and cool to precipitate the title compound as white crystals.

EXAMPLE 9

1 and 2-[6-(2-chloro-4-methoxyphenoxy)hexyl]tetrazole

Stir overnight at room temperature 300 mg. of the iodide prepared in Examples 2 and 3, 3 ml. acetonitrile, 63 mg. 1-H-tetrazole and 274 mg. cesium carbonate in a reaction flask. Add an additional. 189 mg. 1-H-tetrazole and 100 mg. cesium carbonate, let stir one week at room temperature. Work up the reaction mixture in methylene chloride with a water wash. Elute on a coarse silica column with methylene chloride then ethyl acetate/methylene chloride; Isolate two fractions of the title compound, the less polar fraction and the more polar fraction. One of the fractions is the 1-substituted tetrazole and the other fraction is the 2-substituted tetrazole.

EXAMPLE 10

1-[6-(2-chloro-4-methoxyphenoxy)hexyl] -1,2,3,4-tetrahydropyrlmidine-2,4-dione

Stir overnight at room temperature, 300 mg. of the iodide made in Examples 2 or 3, 1 ml. acetonitrile, 274 mg. ceslum carbonate, 270 mg. of 2N-benzoyl uracil, 1 ml. of DMF (to enhance solubility) and 100 mg. additional of cesium carbonate in a reaction flask. Work up in methylene chloride with water and add methanolic potassium carbonate then again stir overnight at room temperature. Work up in methylene chloride with a water wash. Elute on a coarse silica column with methylene chloride and sequently 10%, 20%, 30% and 40% ethyl acetate/methylene chloride to obtain the title compound as an oil which crystallizes upon standing.

EXAMPLE 11

1-[5-(2-chloro-4-methoxyphenoxy)pentyl]imidazole

(a) Prepare 5-[2-chloro-4-methoxyphenoxy)-pentyl-1-iodide by mixing 3 gms. 2-chloro-4-methoxyphenol, 8.7 gms. 1,5-dibromo pentane, and 5.2 gms. potassium carbonate to 75 ml. acetone in a reaction flask. Purge with nitrogen, reflux for 48 hours. Add CH_2Cl_2 and wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with hexane, 10, 15 and 20% CH_2Cl_2/hexane. Isolate product, add 50 ml. acetone, 8.5 g sodium iodide and heat to reflux 10-15 min. Remove acetone, add CH_2Cl_2 and wash with water, then brine and dry over sodium sulfate. Remove solvent and recover the product.

(b) Add 350 mg. of the product of step (a) to 2 ml. DMF (dimethylformamide) and 300 mg. sodium imidazole in a reaction flask. Stir for about 24 hours. Recover the title compound by treating with methylene chloride, a water wash and brine. Dry over sodium sulfate and remove the solvent to obtain a crystalline compound.

Prepare the hydrochloride salt by reacting 275 mg. of the title compound with 10.2 ml. of 0.1N HCl. methylene chloride, wash with water, then brine and recover the title compound by removing the solvent.

The hydrochloride salt is made by reacting the title compound with about 1.1 eq: 0.1N HCl.

EXAMPLE 12

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-hydroxybenzimidazole and N,N'-bis-[6-(2-chloro -4-methoxyphenoxy)hexyl]-2-benzimidazolone

Stir overnight at room temperature, 1 gm. 2 hydroxybenzimidazole, 2 gms. of the iodide prepared in Examples 2 or 3, 0.35 gm sodium hydroxide and 10 ml DMF in a reaction flask. Partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride, then 50/50 methylene chloride/ethylacetate. Two major fractions are obtained, NMR shows the top spot fraction to be N,N'-bis'-[6-(2-chloro-4-methoxyphenoxy)-hexyl]-2-benzimidazolone, FAB-MS: m/z 615 (M^+) free base, H^1-NMR-200 mHz; $^\delta$H ($CDCl_3$), 1.35-1.65 (8H,m), 1.70-1.90 (8H,m), 3.75 (6H,s), 3.80-4.05 (8H,m), 6.7-7.2 (10H,m), and the bottom spot fraction to be 1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-hydroxybenzimidazole. FAB-MS: m/z

375 (M^+); Free Base, H^1-NMR-200 mHz; $^\delta H$ ($CDCl_3$), 1.4-1.70 (4H,m), 1.7-1.9 (4H,m), 3.75 (3H,s), 3.85-4.05 (4H,m), 6.7-7.2 (7H,m).

EXAMPLE 13

9-[6-(2-chloro-4-methoxyphenoxy)hexyl]purine and 7-[6-(2-chloro-4-methoxyphenoxy)hexyl]purine

Stir overnight at room temperature, 300 mg. of the iodide prepared in Examples 2 and 3, 3 ml. DMF, 147 mg. purine and 49 mg. sodium hydroxide in a reaction flask. Add methylene chloride and wash with water. Elute on a coarse silica column with methylene chloride, then 2% methanol/methylene chloride, then 4 and 5% methanol/methylene chloride to obtain a major amount of the 9-substituted title compound and a minor amount of the 7-substituted title compound.

The title compounds do not form water soluble salts.

EXAMPLE 14

1-[7-oxy-7-(4-methoxyphenyl)heptyl]imidazole

(a) Prepare 7-(4-methoxyphenyl-7-oxo)heptyl-1-bromide by stirring for one hour at room temperature, 2.16 gm anisole, 100 ml methylene chloride, 7-bromoheptanoyl chloride and aluminum chloride. Wash with water, sodium bicarbonate solution, water then brine. Dry over sodium sulfate. Elute on a coarse silica column with hexane then methylene chloride/hexane to recover the product.

(b) Heat to reflux for 45 mins. 0.5 gm ofthe product of step (a), 10 ml MEK (methylethylketone) and 1.25 gm sodium iodide. Remove most of the MEK, add methylene chloride, then wash with water, followed by brine and dry over sodium sulfate to give the iodide of the compound prepared in step (a). Add 450 mg of sodium imidazole in 10 ml DMF and stir for 48 hours. Add methylene chloride, wash with water, then wash with brine and dry over sodium sulfate to yield the title compound.

EXAMPLE 15

1-[7-hydroxyimino-7-(4-methoxyphenyl)heptyl] imidazole

Stir overnight at room temperature 0.5 gm of the compound prepared in Example 52(b), 10 ml ethanol, 1 ml water and a large excess of hydroxyl amine•HCl and stir for 4 hours. Remove most of the ethanol by bubbling nitrogen through the reaction mixture. Adjust the pH to about 10 with 10% aqueous NaOH, add methylene chloride and wash with water, then brine and dry over sodium sulfate. Then elute on a coarse silica column with methylene chloride then 1, 2, 3 and 4% methanol/methylene chloride to give the title compound.

Prepare the hydrochloride salt by reaction with 1.1 eq. of 0.1N HCl.

MS: m/z 302 (M^+) HCl salt.

EXAMPLE 16

1-[6-oxy-6-(2,4-dimethoxyphenyl)hexyl]imidazole

(a) Add 1.4 gm 2,4-dimethoxybenzene and 2.2 gm 1-bromohexanoyl chloride to 100 ml methylene chloride. Add 1.3 ml tin chloride and stir for 0.5 hr. Wash with water then 5% sodium bicarbonate to yield 1-[6-oxy-6-(2,4-dimethoxyphenyl)hexyl]bromide.

(b) Add 2.8 gm sodium imidazole in DMF to 3 gm of the compound produced in step (a). Stir for 48 hours, remove DMF, partitition with water/methylene chloride, elute on silica column with 100% methylene chloride then 5% methanol/methylene chloride to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 17

1-[6-hydroxy-6-(2,4-dimethoxyphenyl)hexyl]imidazole

Add 50 ml of ethanol to 1.3 gm of the compound prepared in Example 67, then add 0.5 gm sodium borohydride. Stir for 2.5 hours, remove the solvent, extract with methylene chloride, elute on a silica column with 100% methylene chloride, then 5% methanol/methylene chloride to yield the title compound.

EXAMPLE 18

1-[6-(2,4-dimethoxyphenyl)hex-5-enyl]-imidazole, hydrochloride

Treat 0.266 gm of the compound prepared in Example 68 with 11 ml of 0.1N HCl to give the title compound.

EXAMPLE 19

1-[6-(naphthalene-2-oxy)hexyl]imidazole

(a) Add 5 gm of beta-naphthol to 100 ml methylene chloride then add 27 ml 1,6-dibromohexane followed by 0.5 gm tetra n-butyl ammonium sulfate then 75 ml water and 25 ml of 50% sodium hydroxide. Stir for 48 hours, partition with water/methylene chloride, remove the methylene chloride and distill the residue at 0.1 mm mercury to give the product 1-[6-(naphthalene-2-oxy)hexyl]bromide.
(b) Add 2 gm of the compound produced in step (a) to a solution of 2 gm imidazole and 0.5 gm sodium hydroxide in 20 ml DMF and stir overnight. Remove the solvent, partition with methylene chloride/water. Elute on a silica column with 100% methylene chloride then 5% methanol to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 20

1-[6-(4-methoxyphenylthio)hexyl]imidazole

(a) Add to a reaction flask 10 gm p-mercaptoanisole, 55 ml 1,6-dibromohexane, 150 ml water, 200 ml methylene chloride, 50 ml of 50% sodium hydroxide and finally 2 gm tetra n-butylammonium sulfate and stir overnight. Partition with water/methylene chloride then brine/methylene chloride. Remove excess dibromohexane. Add the resulting residue to hexane, remove crystalline disulfide side product then remove the hexane to obtain 1-[6-(4-methoxyphenylthio)hexyl]bromide.
(b) Dissolve 5 gm imidazole and 1.5 gm sodium hydroxide in DMF. Add 5 gms of the compound prepared in step (a) and stir overnight. Remove the solvent, partition with water/methylene chloride. Elute the methylene chloride. Elute the methylene chloride fraction on a silica column with 100% methylene chloride then with 5% methanol/methylene chloride to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.

EXAMPLE 21

1-[6-(4-methoxyphenylsulfonyl)hexyl]imidazole

Add 3.5 gm of the title compound prepared in Example 78 to 125 ml acetic acid, then add 24 ml of 30% hydrogen peroxide in 2 portions, 24 hours apart, stir for 48 hours. Adjust pH to >10 with 25% sodium hydroxide. Partition with water/methylene chloride. Elute on a silica column using 100% methylene chloride then 5% methanol to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.

Claims

Claims for the f llowing Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

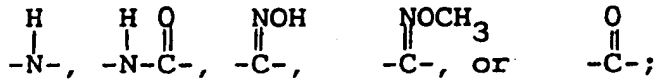
1. A compound respresented by formula I

Z-X-Q-Y-W I

and pharmaceutically acceptable acid addition, basic addition and quarternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein

Z is tetiary butyl, phenyl, naphthyl or adamantyl; substituted phenyl, wherein the substituents are one or more of halogen, C_1-C_{10} alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl, C_1-C_{10} alkyl-sulfonyl, oxazol-2-yl, C_1-C_{10} alkanoyl, benzoyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, phenyl, phenylaminothiocarbonyl, or C_1-C_{10} alkylaminothiocarbonyl; 4 to 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen with the remaining members of the ring being at least one carbon, and optionally sulfur or oxygen, wherein the substituents are one or more of carboxyl, hydroxymethyl, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, phenyl C_1-C_{10} alkyl or naphthyl C_1-C_{10} alkyl;

X and Y are each independently a bond, -O-, -S-, $-SO_2-$,



Q is a C_1-C_{10} alkanediyl-C_4-C_7cycloalkanediyl-C_1-C_{10} alkanediyl, C_2-C_{10} alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tetrahydropyrandiyl or, C_1-C_{10} alkanediyltetrahydrofuranediyl-C_1-C_{10} alkanediyl, wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;

W is a monovalent substituted or unsubstitued phenyl or naphthyl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, C_1-C_{10} alkoxy carbonyl, fluorine, chlorine, iodine, sulfamyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxy, hydroxy C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl C_1-C_{10} alkyl, amino C_1-C_{10} alkyl, carboxy C_1-C_{10} alkyl, guanidino, thioureido, C_1-C_{10} alkylsulfonyl-amino, aminocarbonyl C_1-C_{10} alkyl, allyloxycarbonylmethyl or carbamoyloxy C_1-C_{10} alkyl; with the proviso that W cannot be substituted or unsubstituted isoxazolyl.

2. A compound of Claim 1 represented by the formula

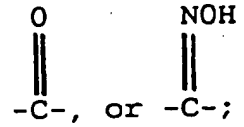
Z^1-X^1-Q^1-W^1

and pharmaceutically acceptable acid addition salts thereof, wherein

Q^1 is alkynediyl of 6, 7 or 8 carbon atoms; or methylcyclohexylmethyl;

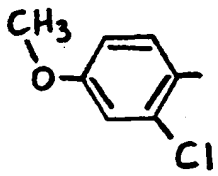
W^1 is unsubstitued or substituted imidazol-1-yl, purin-9-yl, imidazol-2-yl, wherein said substituents are one or more of C_1-C_{10} alkyl, hydroxy C_1-C_{10} alkyl, nitro, C_1-C_{10} alkoxycarbonyl, carboxymethyl or aminocarbonylmethyl;

X^1 is -O-,

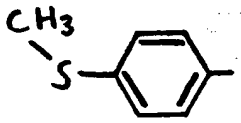


and

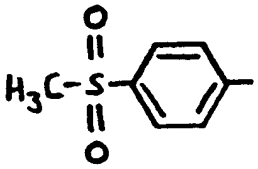
Z^1 is



,



or



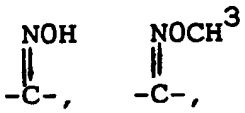
3. A compound of claim 1 represented by the formula

Z^2-X^2-Q^2-Y^2-W^2

and pharmaceutically acceptable acid addition salts or quarternary amine salts thereof, wherein

Z^2 is phenyl; substituted phenyl wherein the substituents are independently one or more of halogen, C_1-C_{10} alkylthio, C_1-C_{10} alkylsulfonyl, C_1-C_{10} alkoxy, oxazol-2-yl, phenoxy; imidazo-1-yl; C_1-C_{10} alkyl substituted imidazo-1-yl; or tert-butyl;

X^2 is a bond, -O-,



-S-,

OR $-SO_2-$

Q^2 is alkynediyl of 6 to 8 carbon atoms; or methylcyclohexylmethyl;

Y^2 is a bond, -S- or $-SO_2-$;

W^2 is imidazol-1-yl; substituted imidazol-1-yl wherein the substituents are independently one or more of C_1-C_{10} alkyl, hydroxyl C_1-C_{10} alkyl, amino C_1-C_{10} alkyl or C_1-C_{10} alkoxycarbonyl; imidazol-2-yl, imidazol-4-yl; imidazol-5-yl; substituted imidazol-2-yl, -4-yl or -5-yl, wherein the substituents are independently one or more of C_1-C_{10} alkyl or alkyloxycarbonyl methyl; pyrrolidin-1-yl; benzimidazol-1-yl; 1,4-dihydro-4-oxo-7-methyl-1,8-3-carboxyl-purin-9-yl; pyridin-2-yl; pyrazol-1-yl; or benzimidazol-2-yl.

4. A compound of claim 1 selected from the group consisting of:
trans 1-[(2-chloro-4-methoxyphenoxy)methyl]4-[(1-imidazolyl)methyl]cyclohexane;
1-(9,9-dimethyl-dec-7-ynyl)-imidazole;
1-[6-(2-chloro-4-methoxyphenoxy)-hex-2-ynyl]imidazole;
1-(8-phenyl-oct-7-ynyl)imidazole;

5. The use of a compound of formula I as defined in any one of claims 1 to 4 for preparing a pharmaceutical composition.

6. A compound of formula I according to any of claims 1-4 for use as an active pharmaceutical substance.

7. A process for producing a compound of formula I as defined in claim 1 characterized in that either:
(A) to produce a compound of formula I, a compound of the formula

$Z\text{-}X\text{-}Q'\text{-}L^1$

wherein Z and X are as defined in claim 1,
Q' is the same as Q defined in claim 1, or, provided Q in formula I is to contain at least one of the groups

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-$$

wherein each R is independently hydrogen or C_1-C_{10} alkyl, Q' may also be the same as Q defined in claim 1 minus at least one of the groups

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-,$$

and
L^1 is a leaving group, with a compound having the formula

$L^2\text{-}Y'\text{-}W''$

wherein L^2 is a leaving group,
W'' is as defined for W in claim 1 or a tautomer thereof, and
Y' is the same as Y defined in claim 1, or, provided Q in formula I is to contain at least one of the groups

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-$$

wherein each R is independently hydrogen or C_1-C_{10} alkyl, Y' may also be the same as Y defined in claim 1 plus at least one of the groups

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-;$$

or
(B) to produce a compound of formula I, at least one compound of the formula

$Z\text{-}X\text{-}Q'\text{-}L^1$

wherein Z, X, Q' and L^1 are as defined above is reacted with a compound of the formula

$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$

wherein L^3 and L^4 are leaving groups,
each Y' is independently as defined above, and
W''' is divalent W' as defined above or
(C) to produce a compound of formula I, wherein Z and W are the same and X and Y are the same, reacting a compound of the formula

L^2-Y'-W''

wherein Y' and W'' are as defined in previously and
L^1 is a leaving group, with a compound of the formula

L^5-Q''-L^6

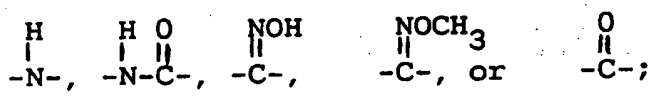
wherein L^5 and L^6 are leaving groups and
Q'' is divalent Q' as defined above, wherein in the above processes, any reactive groups are protected if necessary or desired,
the above processes followed if necessary or desired by
(i) removal of any protecting groups,
(ii) conversion of a compound so produced to another compound of formula I or II,
(iii) if more than one compound of formulas I or II is produced, separation of the compounds so produced, or
(iv) conversion of any of the compounds so produced to an acid addition, basic addition, or quaternary amine salt or pharmaceutically acceptable solvate thereof.

Claims for the following Contracting States : ES, GR

1. A process for producing a compound respresented by formula I

Z-X-Q-Y-W I

and pharmaceutically acceptable acid addition, basic addition and quarternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein
Z is tetiary butyl, phenyl, naphthyl or adamantyl; substituted phenyl, wherein the substituents are one or more of halogen, C_1-C_{10} alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl, C_1-C_{10} alkyl-sulfonyl, oxazol-2-yl, C_1-C_{10} alkanoyl, benzoyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, phenyl, phenylaminothiocarbonyl, or C_1-C_{10} alkylaminothiocarbonyl; 4 to 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen with the remaining members of the ring being at least one carbon, and optionally sulfur or oxygen, wherein the substituents are one or more of carboxyl, hydroxymethyl, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, phenyl C_1-C_{10} alkyl or naphthyl C_1-C_{10} alkyl;
X and Y are each independently a bond, -O-, -S-, -SO_2-,



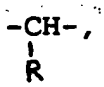
Q is a C_1-C_{10} alkanediyl-C_4-C_7cycloalkanediyl-C_1-C_{10} alkanediyl, C_2-C_{10} alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tetrahydropyrandiyl or, C_1-C_{10} alkanediyltetrahydrofuranediyl-C_1-C_{10} alkanediyl, wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;
W is a monovalent substituted or unsubstitued phenyl or naphthyl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, C_1-C_{10} alkoxy carbonyl, fluorine, chlorine, iodine, sulfamyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxy, hydroxy C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl C_1-C_{10} alkyl, amino C_1-C_{10} alkyl, carboxy C_1-C_{10} alkyl, guanidino, thioureido, C_1-C_{10} alkylsulfonyl-amino, aminocarbonyl C_1-C_{10} alkyl, allyloxycarbonylmethyl or carbamoyloxy C_1-C_{10} alkyl; with the proviso that W cannot be substituted or unsubstituted isoxazolyl, characterised by
(A), reacting a compound of the formula

Z-X-Q'-L^1

wherein Z and X are as defined previously,

Q' is the same as Q defined previously, or, provided Q in formula I is to contain at least one of the groups

wherein each R is independently hydrogen or C_1-C_{10}alkyl, Q' may also be the same as Q defined previously minus at least one of the groups



and

L^1 is a leaving group, with a compound having the formula

L^2-Y'-W''

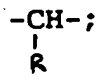
wherein

L^2 is a leaving group,

W'' is as defined for W previously or a tautomer thereof, and

Y' is the same as Y defined previously, or, provided Q in formula I is to contain at least one of the groups

wherein each R is independently hydrogen or C_1-C_{10}alkyl, Y' may also be the same as Y defined previously plus at least one of the groups



or

(B) reacting at least one compound of the formula

Z-X-Q'-L^1

wherein Z, X, Q', and L^1 are as defined previously, with a compound of the formula

L^3-Y'-W'''-Y'-L^4

wherein L^3 and L^4 are leaving groups,

each Y' is independently as defined above, and

W''' is divalent W' as defined above; or

(C) to produce a compound of formula I wherein Z and W are the same and X and Y are the same, reacting a compound of the formula

L^2-Y'-W''

wherein Y' and W'' are as defined previously and

L^2 is a leaving group, with a compound of the formula

L^5-Q''-L^6

wherein L^5 and L^6 are leaving groups and

Q'' is divalent Q' as defined above, wherein in the above processes, any reactive groups are protected if necessary or desired,

the above processes followed if necessary or desired by

(i) removal of any protecting groups,

(ii) conversion of a compound so produced to another compound of formula I,

(iii) if more than one compound of formula I is produced, separation of the compounds so produced, or

(iv) conversion of any of the compounds so produced to an acid addition, basic addition, or quaternary amine salt or pharmaceutically acceptable solvate thereof.

2. A process according to Claim 1 for producing a compound represented by the formula

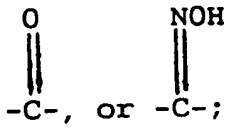
Z^1-X^1-Q^1-W^1

and pharmaceutically acceptable acid addition salts thereof, wherein

Q^1 is alkynediyl of 6, 7 or 8 carbon atoms; or methylcyclohexylmethyl;

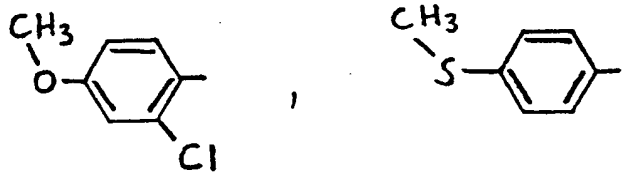
W^1 is unsubstituted or substituted imidazol-1-yl, purin-9-yl, imidazol-2-yl, wherein said substituents are one or more of C_1-C_{10} alkyl, hydroxy C_1-C_{10} akyl, nitro, C_1-C_{10} alkoxycarbonyl, carboxymethyl or aminocarbonylmethyl;

X^1 is -O-,



and

Z^1 is



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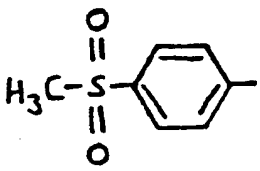


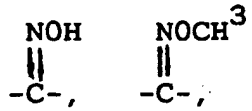
3. A process according to claim 1 for producing a compound represented by the formula

Z^2-X^2-Q^2-Y^2-W^2

and pharmaceutically acceptable acid addition salts or quarternary amine salts thereof, wherein

Z^2 is phenyl; substituted phenyl wherein the substituents are independently one or more of halogen, C_1-C_{10} alkylthio, C_1-C_{10} alkylsulfonyl, C_1-C_{10} alkoxy, oxazol-2-yl, phenoxy; imidazo-1-yl; C_1-C_{10} alkyl substituted imidazo-1-yl; or tert-butyl;

X^2 is a bond, -O-,



-S-,

OR $-SO_2-$

Q^2 is alkynediyl of 6 to 8 carbon atoms; or methylcyclohexylmethyl;

Y^2 is a bond, -S- or $-SO_2-$;

W^2 is imidazol-1-yl; substituted imidazol-1-yl wherein the substituents are independently one or more of C_1-C_{10} alkyl, hydroxyl C_1-C_{10} alkyl, amino C_1-C_{10} alkyl or C_1-C_{10} alkoxycarbonyl; imidazol-2-yl, imidazol-4-yl; imidazol-5-yl; substituted imidazol-2-yl, -4-yl or -5-yl, wherein the substituents are independently one or more of C_1-C_{10} alkyl or alkyloxycarbonyl methyl; pyrrolidin-1-yl; benzimidazol-1-yl; 1,4-dihydro-4-oxo-7-methyl-1,8-3-carboxyl-purin-9-yl; pyridin-2-yl; pyrazol-1-yl; or benzimidazol-2-yl.

4. A process according to claim 1 for producing a compound selected from the group consisting of:
trans 1-[(2-chloro-4-methoxyphenoxy)hexyl]-4,5-[(1-imidazolyl)methyl]cyclohexane;
1-(9,9-dimethyl-dec-7-ynyl)-imidazole
1-[6-(2-chloro-4-methoxyphenoxy)-hex-2-ynyl]imidazole;
1-(8-phenyl-oct-7-ynyl)imidazole;

5. The use of a compound of formula I as defined in any one of claims 1 to 4 for preparing a pharmaceutical composition.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

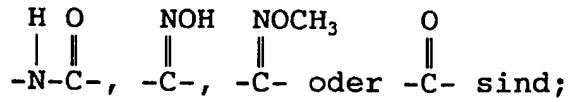
1. Verbindung, welche durch Formel I

Z-X-Q-Y-W I

dargestellt wird, und deren pharmazeutisch annehmbare Säureadditions-, Basenadditions- und quarternäre Aminsalze und deren pharmazeutisch annehmbare Solvate, worin

Z tertiäres Butyl, Phenyl, Naphthyl oder Adamantyl; substituiertes Phenyl, worin die Substituenten einer oder mehrere aus Halogen, C_1-C_{10}-Alkoxy, Phenoxy, Nitril, Nitro, Phenylsulfonyl, C_1-C_{10}-Alkylsulfonyl, Oxazol-2-yl, C_1-C_{10}-Alkanoyl, Benzoyl, C_1-C_{10}-Alkoxycarbonyl, C_1-C_{10}-Alkyl, C_1-C_{10}-Alkylthio, Phenyl, Phenylaminothiocarbonyl oder C_1-C_{10}-Alkylaminothiocarbonyl; ein 4- bis 6-gliedriger, unsubstituierter oder substituierter, heterocyclischer Ring ist, der wenigstens einen Stickstoff, wobei wenigstens eines der restlichen Ringglieder Kohlenstoff ist, und gegebenenfalls Schwefel oder Sauerstoff enthält, worin die Substituenten einer oder mehrere aus Carboxyl, Hydroxymethyl, C_1-C_{10}-Alkyl, C_1-C_{10}-Alkylcarbonyl, Phenyl-C_1-C_{10}-alkyl oder Naphthyl-C_1-C_{10}-alkyl ist;

X und Y jeweils unabhängig eine Bindung, -O-, -S-, $-SO_2-$,

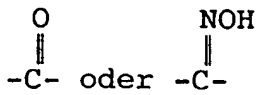


Q C_1-C_{10}-Alkandiyl-C_4-C_7-cycloalkandiyl-C_1-C_{10}-alkandiyl, C_2-C_{10}-Alkindiyl, Phenylen, Dihydrofurandiyl, Tetrahydrofurandiyl, Tetrahydropyrandiyl oder C_1-C_{10}-Alkandiyltetrahydrofurandiyl-C_1-C_{10}-alkandiyl ist, worin die Substituenten einer oder mehrere aus Hydroxy, Epoxy, Fluor, Chlor, Azid oder Amino sind;
W eine einwertige, substituierte oder unsubstituierte Phenyl- oder Naphthylgruppe oder ein heterocyclischer, einzelner oder kondensierter, 4 bis 10 Ringatome enthaltender Ring ist, wovon wenigstens ein Heteroatom ein Stickstoffatom ist und wenigstens eines der restlichen Ringatome Kohlenstoff und gegebenenfalls Schwefel oder Sauerstoff ist, worin die Substituenten einer oder mehrere aus Hydroxy, Oxo, Amino, Carbamoyl, Carboxyl, Nitril, Nitro, C_1-C_{10}-Alkoxycarbonyl, Fluor, Chlor, Iod, Sulfamyl, C_1-C_{10}-Alkyl, C_1-C_{10}-Alkylthio, C_1-C_{10}-Alkoxy, Hydroxy-C_1-C_{10}-alkyl, C_1-C_{10}-Alkoxycarbonyl-C_1-C_{10}-alkyl, Amino-C_1-C_{10}-alkyl, Carboxy-C_1-C_{10}-alkyl, Guanidino, Thioureido, C_1-C_{10}-Alkylsulfonylamino, Aminocarbonyl-C_1-C_{10}-alkyl, Allyloxycarbonylmethyl oder Carbamoyloxy-C_1-C_{10}-alkyl sind, mit der Maßgabe, daß W nicht substituiertes oder unsubstituiertes Isoxazolyl sein kann.

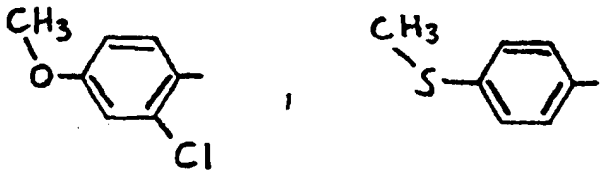
2. Verbindung des Anspruchs 1, welche durch die Formel

Z^1-X^1-Q^1-W^1

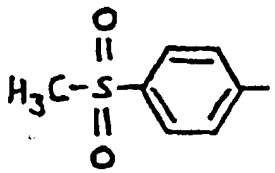
dargestellt wird, und deren pharmazeutisch annehmbare Säureadditionssalze, worin
Q^1 Alkindiyl mit 6, 7 oder 8 Kohlenstoffatomen oder Methylcyclohexylmethyl ist;
W^1 unsubstituiertes oder substituiertes Imidazol-1-yl, Purin-9-yl, Imidazol-2-yl ist, worin die Substituenten einer oder mehrere aus C_1-C_{10}-Alkyl, Hydroxy-C_1-C_{10}-alkyl, Nitro, C_1-C_{10}-Alkoxycarbonyl, Carboxymethyl oder Aminocarbonylmethyl ist;
X^1 -O-,



ist und
Z^1



oder

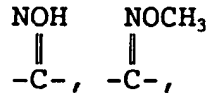


ist.

3. Verbindung des Anspruchs 1, welche durch die Formel

Z^2-X^2-Q^2-Y^2-W^2

dargestellt wird, und deren pharmazeutisch annehmbare Säureadditionssalze oder quarternären Aminsalze, worin
Z^2 Phenyl; substituiertes Phenyl, worin die Substituenten unabhängig einer oder mehrere aus Halogen, C_1-C_{10}-Alkylthio, C_1-C_{10}-Alkylsulfonyl, C_1-C_{10}-Alkoxy, Oxazol-2-yl, Phenoxy sind; Imidazol-1-yl; C_1-C_{10}-alkylsubstituiertes Imidazol-1-yl oder tert-Butyl ist;
X^2 eine Bindung, -O-,



-S-,

oder $-SO_2-$ ist;
Q^2 Alkindiyl mit 6 bis 8 Kohlenstoffatomen oder Methylcyclohexylmethyl ist;
Y^2 eine Bindung, -S- oder $-SO_2-$ ist;
W^2 Imidazol-1-yl; substituiertes Imidazol-1-yl, worin die Substituenten unabhängig einer oder mehrere aus C_1-C_{10}-Alkyl, Hydroxy-C_1-C_{10}-alkyl, Amino-C_1-C_{10}-alkyl oder C_1-C_{10}-Alkoxycarbonyl sind; Imidazol-2-yl, Imidazol-4-yl; Imidazol-5-yl; substituiertes Imidazol-2-yl, -4-yl oder -5-yl, worin die Substituenten unabhängig einer oder mehrere aus C_1-C_{10}-Alkyl oder Alkyloxycarbonylmethyl sind; Pyrrolidin-1-yl; Benzimidazol-1-yl; 1,4-Dihydro-4-oxo-7-methyl-1,8-3-carboxylpurin-9-yl; Pyridin-2-yl; Pyrazol-1-yl oder Benzimidazol-2-yl ist.

4. Verbindung des Anspruchs 1, welche aus der Gruppe ausgewählt ist, die aus
trans-1-[(2-Chlor-4-methoxyphenoxy)methyl]-4-[(1-imidazolyl)methyl]cyclohexan,
1-(9,9-Dimethyl-dec-7-inyl)-imidazol,
1-[6-(2-Chlor-4-methoxyphenoxy)-hex-2-inyl]imidazol,
1-(8-Phenyloct-7-inyl)imidazol
besteht.

5. Verwendung einer wie in irgendeinem der Ansprüche 1 bis 4 definierten Verbindung der Formel I zum Herstellen einer pharmazeutischen Zusammens tzung.

6. Verbindung der Formel I gemäß irgendeinem der Ansprüche 1 bis 4 zur Verwendung als pharmazeutisch aktive Substanz.

7. Verfahren zum Herstellen einer Verbindung der in Anspruch 1 definierten Formel I, dadurch gekennzeichnet, daß entweder
(A) zum Herstellen einer Verbindung der Formel I, eine Verbindung der Formel

$Z\text{-}X\text{-}Q'\text{-}L^1$

worin Z und X wie in Anspruch 1 definiert sind,
Q' dasselbe wie in Anspruch 1 definiertes Q ist, oder, vorausgesetzt, daß Q in Formel I wenigstens eine der Gruppen

enthält, worin jedes R unabhängig Wasserstoff oder C_1-C_{10}-Alkyl ist, Q' auch dasselbe wie in Anspruch 1 definiertes Q abzüglich wenigstens einer der Gruppen

sein kann und L^1 eine Abgangsgruppe ist, mit einer Verbindung der Formel

$L^2\text{-}Y'\text{-}W''$

umgesetzt wird, worin L^2 eine Abgangsgruppe ist,
W'' wie in Anspruch 1 definiertes W oder ein Tautomer desselben ist und
Y' dasselbe wie in Anspruch 1 definiertes Y ist, oder, vorausgesetzt, daß Q in Formel I wenigstens eine der Gruppen

enthält, worin jedes R unabhängig Wasserstoff oder C_1-C_{10}-Alkyl ist, Y' auch dasselbe wie in Anspruch 1 definiertes Y zuzüglich wenigstens einer der Gruppen

sein kann, oder
(B) zum Herstellen einer Verbindung der Formel I, wenigstens eine Verbindung der Formel

$Z\text{-}X\text{-}Q'\text{-}L^1$

worin Z, X, Q' und L^1 wie vorstehend definiert sind, mit einer Verbindung der Formel

$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$

umgesetzt wird, worin L^3 und L^4 Abgangsgruppen sind, jedes Y' unabhängig wie vorstehend definiert ist und W''' vorstehend definiertes, zweiwertiges W' ist, oder
(C) zum Herstellen einer Verbindung der Formel I, worin Z und W dasselbe sind und X und Y dasselbe sind, eine Verbindung der Formel

L^2-Y'-W''

worin Y' und W''' wie zuvor definiert sind und L^2 eine Abgangsgruppe ist, mit einer Verbindung der Formel

L^5-Q''-L^6

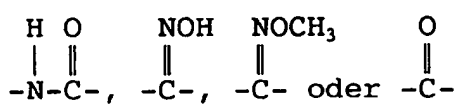
umgesetzt wird, worin L^5 und L^6 Abgangsgruppen sind und Q'' wie vorstehend definiertes, zweiwertiges Q' ist, wobei in den vorstehenden Verfahren irgendwelche reaktionsfähigen Gruppen nötigenfalls oder gewünschtenfalls geschützt sind und die vorstehenden Verfahren nötigenfalls oder gewünschtenfalls von der
(i) Entfernung irgendwelcher Schutzgruppen,
(ii) Überführung einer so gebildeten Verbindung in eine weitere Verbindung der Formel I oder II,
(iii) falls mehr als eine Verbindung der Formeln I oder II hergestellt wird, Trennung der auf diese Weise hergestellten Verbindungen, oder
(iv) Überführung irgendwelcher, auf diese Weise hergestellter Verbindungen in deren Säureadditions-, Basenadditions- oder quarternäres Aminsalz oder pharmazeutisch annehmbares Solvat gefolgt werden.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung, welche durch Formel I

Z-X-Q-Y-W I

dargestellt wird, und deren pharmazeutisch annehmbare Säureadditions-, Basenadditions- und quarternäre Aminsalze und deren pharmazeutisch annehmbare Solvate, worin
Z tertiäres Butyl, Phenyl, Naphthyl oder Adamantyl; substituiertes Phenyl, worin die Substituenten einer oder mehrere aus Halogen, C_1-C_{10}-Alkoxy, Phenoxy, Nitril, Nitro, Phenylsulfonyl, C_1-C_{10}-Alkylsulfonyl, Oxazol-2-yl, C_1-C_{10}-Alkanoyl, Benzoyl, C_1-C_{10}-Alkoxycarbonyl, C_1-C_{10}-Alkyl, C_1-C_{10}-Alkylthio, Phenyl, Phenylaminothiocarbonyl oder C_1-C_{10}-Alkylaminothiocarbonyl; ein 4- bis 6-gliedriger, unsubstituierter oder substituierter, heterocyclischer Ring ist, der wenigstens einen Stickstoff, wobei wenigstens eines der restlichen Ringglieder Kohlenstoff ist, und gegebenenfalls Schwefel oder Sauerstoff enthält, worin die Substituenten einer oder mehrere aus Carboxyl, Hydroxymethyl, C_1-C_{10}-Alkyl, C_1-C_{10}-Alkylcarbonyl, Phenyl-C_1-C_{10}-alkyl oder Naphthyl-C_1-C_{10}-alkyl ist;
X und Y jeweils unabhängig eine Bindung, -O-, -S-, $-SO_2$-,



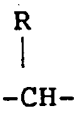
sind;
Q C_1-C_{10}-Alkandiyl-C_4-C_7-cycloalkandiyl-C_1-C_{10}-alkandiyl, C_2-C_{10}-Alkindiyl, Phenylen, Dihydrofurandiyl, Tetrahydrofurandiyl, Tetrahydropyrandiyl oder C_1-C_{10}-Alkandiyltetrahydrofurandiyl-C_1-C_{10}-alkandiyl

ist, worin die Substituenten einer oder mehrere aus Hydroxy, Epoxy, Fluor, Chlor, Azid oder Amino sind;
W eine einwertige, substituierte oder unsubstituierte Phenyl- oder Naphthylgruppe oder ein heterocyclischer, einzelner oder kondensierter, 4 bis 10 Ringatome enthaltender Ring ist, wovon wenigstens ein Heteroatom ein Stickstoffatom ist und wenigstens eines der restlichen Ringatome Kohlenstoff und gegebenenfalls Schwefel oder Sauerstoff ist, worin die Substituenten einer oder mehrere aus Hydroxy, Oxo, Amino, Carbamoyl, Carboxyl, Nitril, Nitro, C_1-C_{10}-Alkoxycarbonyl, Fluor, Chlor, Iod, Sulfamyl, C_1-C_{10}-Alkyl, C_1-C_{10}-Alkylthio, C_1-C_{10}-Alkoxy, Hydroxy-C_1-C_{10}-alkyl, C_1-C_{10}-Alkoxycarbonyl-C_1-C_{10}-alkyl, Amino-C_1-C_{10}-alkyl, Carboxy-C_1-C_{10}-alkyl, Guanidino, Thioureido, C_1-C_{10}-Alkylsulfonylamino, Aminocarbonyl-C_1-C_{10}-alkyl, Allyloxycarbonylmethyl oder Carbamoyloxy-C_1-C_{10}-alkyl sind, mit der Maßgabe, daß W nicht substituiertes oder unsubstituiertes Isoxazolyl sein kann, gekennzeichnet durch

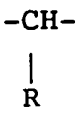
(A) Umsetzen einer Verbindung der Formel

$$Z\text{-}X\text{-}Q'\text{-}L^1$$

worin Z und X wie zuvor definiert sind,
Q' dasselbe wie zuvor definiertes Q ist, oder, vorausgesetzt, daß Q in Formel I wenigstens eine der Gruppen



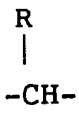
enthält, worin jedes R unabhängig Wasserstoff oder C_1-C_{10}-Alkyl ist, Q' auch dasselbe wie zuvor definiertes Q abzüglich wenigstens einer der Gruppen



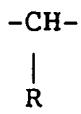
sein kann und L^1 eine
Abgangsgruppe ist, mit einer Verbindung der Formel

$$L^2\text{-}Y'\text{-}W''$$

worin L^2 eine Abgangsgruppe ist,
W'' wie zuvor definiertes W oder ein Tautomer desselben ist und Y' dasselbe wie zuvor definiertes Y ist, oder, vorausgesetzt, daß Q in Formel I wenigstens eine der Gruppen



enthält, worin jedes R unabhängig Wasserstoff oder C_1-C_{10}-Alkyl ist, Y' auch dasselbe wie zuvor definiertes Y zuzüglich wenigstens einer der Gruppen



sein kann, oder

(B) Umsetzen wenigstens einer Verbindung der Formel

$Z\text{-}X\text{-}Q'\text{-}L^1$

worin Z, X, Q' und L^1 wie zuvor definiert sind, mit einer Verbindung der Formel

$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$

worin L^3 und L^4 Abgangsgruppen sind, jedes Y' unabhängig wie vorstehend definiert ist und W''' vorstehend definiertes, zweiwertiges W' ist, oder
(C) zum Herstellen einer Verbindung der Formel I, worin Z und W dasselbe sind und X und Y dasselbe sind, eine Verbindung der Formel

$L^2\text{-}Y'\text{-}W''$

worin Y' und W''' wie zuvor definiert sind und L^2 eine Abgangsgruppe ist, mit einer Verbindung der Formel

$L^5\text{-}Q''\text{-}L^6$

umgesetzt wird, worin L^5 und L^6 Abgangsgruppen sind und Q'' wie vorstehend definiertes, zweiwertiges Q' ist, wobei in den vorstehenden Verfahren irgendwelche reaktionsfähigen Gruppen nötigenfalls oder gewünschtenfalls geschützt sind und die vorstehenden Verfahren nötigenfalls oder gewünschtenfalls von der

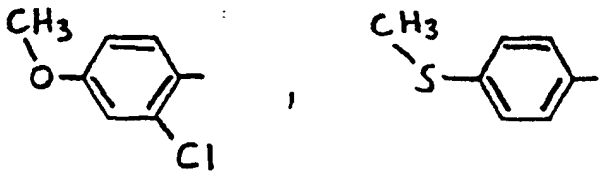
(i) Entfernung irgendwelcher Schutzgruppen,
(ii) Überführung einer so gebildeten Verbindung in eine weitere Verbindung der Formel I oder II,
(iii) falls mehr als eine Verbindung der Formeln I oder II hergestellt wird, Trennung der auf diese Weise hergestellten Verbindungen, oder
(iv) Überführung irgendwelcher, auf diese Weise hergestellter Verbindungen in deren Säureadditions-, Basenadditions- oder quarternäres Aminsalz oder pharmazeutisch annehmbares Solvat gefolgt werden.

2. Verfahren gemäß Anspruch 1 zum Herstellen einer Verbindung, welche durch die Formel

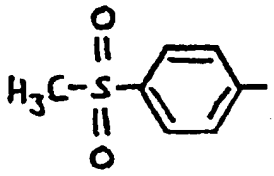
$Z^1\text{-}X^1\text{-}Q^1\text{-}W^1$

dargestellt wird, und deren pharmazeutisch annehmbarer Säureadditionssalze, worin
Q^1 Alkindiyl mit 6, 7 oder 8 Kohlenstoffatomen oder Methylcyclohexylmethyl ist;
W^1 unsubstituiertes oder substituiertes Imidazol-1-yl, Purin-9-yl, Imidazol-2-yl ist, worin die Substituenten einer oder mehrere aus C_1-C_{10}-Alkyl, Hydroxy-C_1-C_{10}-alkyl, Nitro, C_1-C_{10}-Alkoxycarbonyl, Carboxymethyl oder Aminocarbonylmethyl ist;
X^1 -O-,

ist und
Z^1



oder

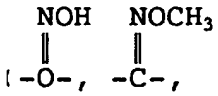


ist.

3. Verfahren gemäß Anspruch 1 zum Herstellen einer Verbindung, welche durch die Formel

Z^2-X^2-Q^2-Y^2-W^2

dargestellt wird, und deren pharmazeutisch annehmbarer Säureadditionssalze oder quarternären Aminsalze, worin
Z^2 Phenyl; substituiertes Phenyl, worin die Substituenten unabhängig einer oder mehrere aus Halogen, C_1-C_{10}-Alkylthio, C_1-C_{10}-Alkylsulfonyl, C_1-C_{10}-Alkoxy, Oxazol-2-yl, Phenoxy sind; Imidazol-1-yl; C_1-C_{10}-alkylsubstituiertes Imidazol-1-yl oder tert-Butyl ist;
X^2 eine Bindung,



-C-,

-C- oder -SO_2- ist;
Q^2 Alkindiyl mit 6 bis 8 Kohlenstoffatomen oder Methylcyclohexylmethyl ist;
Y^2 eine Bindung, -S- oder -SO_2- ist;
W^2 Imidazol-1-yl; substituiertes Imidazol-1-yl, worin die Substituenten unabhängig einer oder mehrere aus C_1-C_{10}-Alkyl, Hydroxy-C_1-C_{10}-alkyl, Amino-C_1-C_{10}-alkyl oder C_1-C_{10}-Alkoxycarbonyl sind; Imidazol-2-yl, Imidazol-4-yl; Imidazol-5-yl; substituiertes Imidazol-2-yl, -4-yl oder -5-yl, worin die Substituenten unabhängig einer oder mehrere aus C_1-C_{10}-Alkyl oder Alkyloxycarbonylmethyl sind; Pyrrolidin-1-yl; Benzimidazol-1-yl; 1,4-Dihydro-4-oxo-7-methyl-1,8-3-carboxylpurin-9-yl; Pyridin2-yl; Pyrazol-1-yl oder Benzimidazol-2-yl ist.

4. Verfahren gemäß Anspruch 1 zum Herstellen einer Verbindung, welche aus der Gruppe ausgewählt ist, die aus
trans-1-[(2-Chlor-4-methoxyphenoxy)methyl]-4-[(1-imidazolyl)methyl]cyclohexan,
1-(9,9-Dimethyl-dec-7-inyl)-imidazol,
1-[6-(2-Chlor-4-methoxyphenoxy)-hex-2-inyl]imidazol,
1-(8-Phenyloct-7-inyl)imidazol
besteht.

5. Verwendung einer wie in irgendeinem der Ansprüche 1 bis 4 definierten Verbindung der Formel I zum Herstellen einer pharmazeutischen Zusammensetzung.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

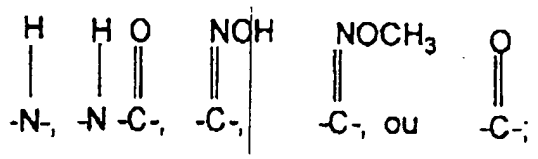
1. Composé représenté par la formule I

Z-X-Q-Y-W I

et ses sels d'addition d'acide, d'addition basique et d'amine quaternaire acceptables en pharmacie ainsi que ses solvats acceptables en pharmacie, où

Z est butyle tertiaire, phényle, naphtyle ou adamantyle; phényle substitué, où les substituants sont un ou plusieurs parmi halogène, alcoxy C_1-C_{10}, phénoxy, nitrile, nitro, phénylsulfonyle, alkyl C_1-C_{10}-sulfony, oxazol-2-yle, alkanoyle C_1-C_{10}, benzoyle, alcoxycarbonyl-C_1-C_{10}, alkyle C_1-C_{10}, alkylthio C_1-C_{10}, phényle, phényl-aminothiocarbonyle, ou alkylaminothiocarbonyle C_1-C_{10}; un noyau hétérocyclique de 4 à 6 membres, non substitué ou substitué, contenant au moins un azote, les membres restants du noyau étant formés d'au moins un carbone et facultativement du soufre ou de l'oxygène, ou les substituants sont un ou plusieurs parmi carboxyle, hydroxyméthyle, alkyle C_1-C_{10}, alkylcarbonyle C_1-C_{10}, phényl alkyle C_1-C_{10} ou naphtyl alkyle C_1-C_{10};

chacun des X et Y est indépendamment une liaison, -O-, -S-, $-SO_2$-,



Q est un alcynediyl C_1-C_{10} -cycloalcanediyl-C_4-C_7-alcanediyle C_1-C_{10}, alcynediyle C_2-C_{10}, phénylène, dihydrofurandiyle, tétrahydrofurandiyle, tétrahydropyrandiyle ou alcanediyltétrahydrofurandiyle-C_1-C_{10}- alkanédiyle, où les substituants sont un ou plusieurs parmi hydroxy, epoxy, fluor, chlore, azide ou amino;

W est un groupe phényle ou naphtyle monovalent substitué ou non substitué ou bien un noyau hétérocyclique simple ou fusionné contenant 4 à 10 atomes dans le noyau, dont au moins un hétéroatome est un atome d'azote et les atomes restants du noyau sont au moins un carbone et facultativement du soufre ou de l'oxygène, où les substitants sont un ou plusieurs parmi hydroxy, oxo, amino, carbamoyle, carboxyle, nitrile, nitro, alcoxy C_1-C_{10} carbonyle, fluor, chlore, iode, sulfamyle, alkyle C_1-C_{10}, alkylthio C_1-C_{10}, alcoxy C_1-C_{10}, hydroxy alkyl C_1-C_{10}, alcoxycarbonyle C_1-C_{10}, alkyle C_1-C_{10}, amino, alkyle C_1-C_{10}, carboxy alkyle C_1-C_{10}, guanidino, thioureido, alkylsulfonyl C_1-C_{10}-amino, aminocarbonyl-alkyle C_1-C_{10}, allyloxycarbonylméthyle ou carbamoyloxy alkyle C_1-C_{10}; à condition que W ne puisse être isoxazolyle substitué ou non substitué.

2. Composé de la ravondication 1, représenté par la formule

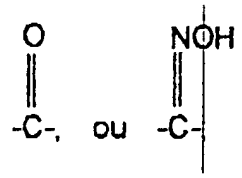
Z^1-X^1-Q^1-W^1

et ses sels d'addition d'acide acceptables en pharmacie, où

Q1 est alcynediyle de 6, 7 ou 8 atomes de carbone; ou bien méthylcyclohéxylméthyle;

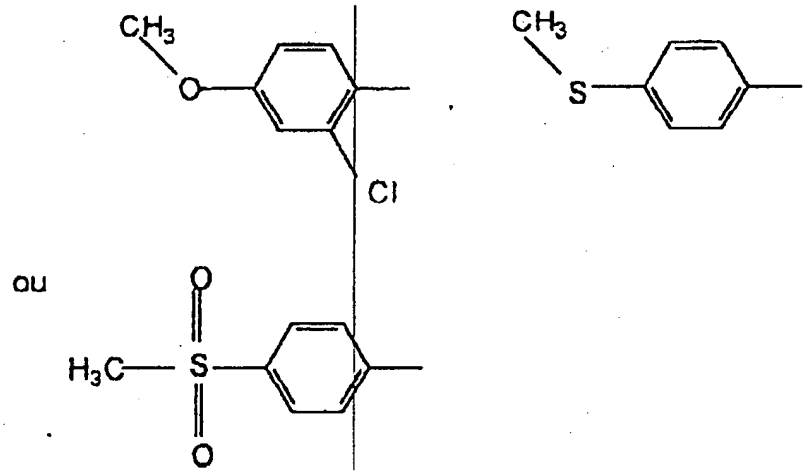
W^1 est imidazol-1-yle, purin-9-yle, imidazol-2-yle, non substitués ou substitués, où lesdits substituants bont un ou plusieurs parmi alkyle C_1-C_{10}, hydroxy alkyle C_1-C_{10}, nitro, alcoxycarbonyle C_1-C_{10}, carboxyméthyle ou aminocarbonylméthyle;

X^1 est -O-,



et

Z^1 est



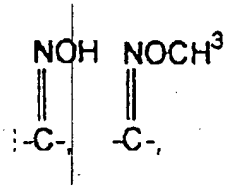
3. Composé de la revendication 1 représenté par la formule

Z^2-X^2-Q^2-Y^2-W^2

et ses sels d'addition acide ou sels d'amine quaternaire acceptables en pharmacie, ou

Z^2 est phényle; phényle substitué ou les substituants sont indépendamment un ou plusieurs parmi halogène, alkylthio C_1-C_{10}, alkylsulfonyle C_1-C_{10}, alcoxy C_1-C_{10}, oxazol-2-yle, phénoxy; imidazol-1-yle; imidazol-1-yle substitué par alkyle C_1-C_{10} ou butyle tertiaire;

X^2 est une liaison, -O-,



-S-,

ou $-SO_2-$

Q^2 est alcynediyle de 6 à 8 atomes de carbone; ou bien méthylcyclohexylméthyle;

Y^2 est une liaison, -S- ou $-SO_2-$;

W^2 est imidazol-1-yle; imidazol-1-yle substitué ou les substituants sont indépendamment un ou

plusieurs parmi alkyle C_1-C_{10}, hydroxyl alkyle C_1-C_{10}, amino alkyle C_1-C_{10}, ou alcoxycarbonyle C_1-C_{10}; imidazol-2-yle, imidazol-4-yle, imidazol-5-yle; imidazol-2-yle, -4-yle ou -5-yle substitués, où les substituants sont indépendamment un ou plusieurs parmi alkyle C_1-C_{10} ou alkyloxycarbonyle méthyle; pyrrolidin-1-yle; benzimidazol-1-yle; 1,4-dihydro-4-oxo-7-méthyl-1,8-3-carboxyl-purin-9-yle; pyridin-2-yle;
pyrazol-1-yle; ou benzimidazol-2-yle.

4. Composé de la revendication 1 choisi dans le groupe consistant en :
trans 1-[(2-chloro-4-méthoxyphénoxy)méthyl]4-[(1-imidazolyl)méthyl]cyclohexane;
1-(9,9-diméthyl-dec-7-ynyl)-imidazole;
1-[6-(2-chloro-4-méthoxyphénoxy)-hex-2-ynyl]imidazole;
1-(8-phényl-oct-7-ynyl)imidazole;

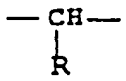
5. Utilisation d'un composé de formule I tel que défini selon l'une quelconque des revendications 1 à 4 pour la préparation d'une composition pharmaceutique.

6. Composé de formule I selon l'une quelconque des revendications 1-4 pour une utilisation en tant que substance pharmaceutique active.

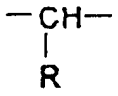
7. Procédé de production d'un composé de formule I tel que défini à la revendlcation 1, caractérisé en ce que soit :
(A) pour produire un composé de formule I, on fait réagir un composé de la formule

Z-X-Q'-L^1

où Z et X sont tels que définis à la revendication 1,
Q' est comme Q défini à la revendication 1, ou à condition que Q dans la formule I doive contenir au moins l'un des groupes



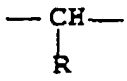
où chaque R est indépendamment hydrogène ou alkyle C_1-C_{10}, Q' peut également être comme Q défini à la revendication 1 moins au moins l'un des groupes



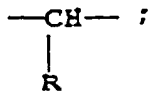
et L^1 est un groupe partant, avec un composé ayant pour formule

L^2-Y'-W''

où L^2 est un groupe partant,
W'' est tel que défini pour W à la revendication 1 ou bien son tautomère et
Y' est le même que Y défini à la revendication 1, ou, à condition que Q dans la formule I doive contenir au moins l'un des groupes



où chaque R est indépendamment hydrogène ou alkyle C_1-C_{10}, Y' peut également être le même que Y défini à la revendication 1, plus au moins l'un des groupes



ou

(B) pour produire un composé de formule I, on fait réagir au moins un composé de la formule

Z-X-Q'-L^1

où Z, X, Q' et L^1 sont tels que définis ci-dessus, avec un composé de la formule

L^3-Y'-W'''-Y'-L^4

où L^3 et L^4 sont des groupes partants,
chaque Y' est indépendamment tel que défini ci-dessus, et
W''' est W' divalent tel que défini ci-dessus ou

(C) pour produire un composé de formule I, où Z et W sont identiques et X et Y sont identiques, la réaction d'un composé de la formule

L^2-Y'-W''

où Y' et W'' sont tels ue définis précédemment et
L^1 est un groupe partant, avec un composé de la formule

L^5-Q''-L^6

où L^5 et L^6 sont des groupes partants et
Q'' est Q' divalent défini ci-dessus, où, dans les procédés ci-dessus, tous les groupes réactifs sont protégés si nécessaire ou si on le souhaite,
les procédés ci-dessus étant suivis si nécessaire ou si on le souhaite par
(i) l'élimination de tous les groupes protecteurs
(ii) la convarsion d'un composé ainsi produit en un autre composé de formule I ou II,
(iii) si l'on produit plus d'un composé des formules I ou II, la séparation des composés ainsi produit, ou
(iv) la conversion de chacun des composés ainsi produits en un sel d'addition d'acide, d'addition basique ou quaternaire ou bien un solvat acceptable en pharmacie.

Revendications pour les Etats contractants suivants : ES, GR

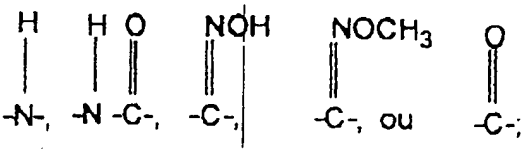
1. Procédé de production d'un composé représenté par la formule I

Z-X-Q-Y-W I

et ses sels d'addition d'acide, d'addition basique et d'amine quarternaire acceptables en pharmacie ainsi que ses solvants acceptables en pharmacie, où

Z est butyle tertiaire phényle, naphtyle ou adamantyle; phényle substitué, où les substituants sont un ou plusieurs parmi halogène, alcoxy C_1-C_{10}, phénory, nitrile, nitro, phénylsulfonyle, alkyl C_1-C_{10}-sulfonyle, oxazol-2-yle, alkanoyle C_1-C_{10}, benzoyle, alcoxycarbonyle C_1-C_{10}, alkyle C_1-C_{10}, alkylthio C_1-C_{10}, phényle, phényl-aminothiocarbonyle, ou alkylaminothiocarbonyle C_1-C_{10}; un noyau hétérocyclique de 4 à 6 membres, non substitué ou substitué, contenant au moins un azote, les membres restants du noyau étant formés d'au moins un carbone et facultativement du soufre ou de l'oxygène, où les substituants sont un ou plusieurs parmi carboxyle, hydroxyméthyle, alkyle C_1-C_{10}, alkylcarbonyle C_1-C_{10}, phényl alkyle C_1-C_{10} ou naphtyl alkyle C_1-C_{10};

chacun de X et Y est indépendamment une liaison, -O-, -S-, -SO_2-,



Q est un alcanediyl C_1-C_{10} -cycloalcanediyl C_4-C_7-alcanediyle C_1-C_{10}, alcynediyle C_2-C_{10}, phénylène, dihydrofurandiyle, tétrahydrofurandiyle, tétrahydropyrandiyle ou alcanediyltétrahydrofurandiyle-C_1-C_{10}- alcanediyle, C_1-C_{10} où les substituants sont un ou plusieurs parmi hydroxy, époxy, fluor, chlore, azide ou amino;

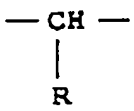
W est un groupe phényle ou naphtyle monovalent substitué ou non substitué ou bien un noyau hétérocyclique simple ou fusionné contenant 4 à 10 atomes dans le noyau, dont au moins un hétéroatome est un atome d'azote et les atomes restants du noyeu sont au moins un carbone et facultativement du soufre ou de l'oxygène, où les substitants sont un ou plusieurs parmi hydroxy, oxo, amino, carbamoyle, carboxyle, nitrile, nitro, alcoxy C_1-C_{10} carbonyle, fluor, chlore, iode, sulfamyle, alkyle C_1-C_{10}, alkylthio C_1-C_{10}, alcoxy C_1-C_{10}, hydroxy alkyle C_1-C_{10}, alcoxycarbonyle C_1-C_{10}, alkyle C_1-C_{10}, amino alkyle C_1-C_{10}, carboxy alkyle C_1-C_{10}, guanidino, thiouréido, alkylsulfonyl C_1-C_{10}- amino, aminocarbonyl-alkyle C_1-C_{10}, allyloxycarbonylméthyle ou carbamoyloxy alkyle C_1-C_{10}; à condition que W ne puisse être isoxazolyle substitué ou non substitué, caractérisé par

(A), la réaction d'un composé de la formule

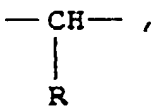
$Z\text{-}X\text{-}Q'\text{-}L^1$

où Z et X sont tels que définis précédemment,

Q' est comme Q défini précédemment ou, à condition que Q dans la formule puisse contenir au moins l'un des groupes



où chaque R est independamment hydrogène ou alkyle C_1-C_{10}, Q' peut également être code Q défini précédemment moins au moins l'un des groupes



et

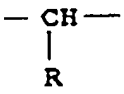
L^1 est un groupe partant, avec un composé ayant pour formule

$L^2\text{-}Y'\text{-}W''$

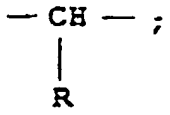
où L^2 est un groupe partant,

W'' est tel que défini pour W précédemment ou bien son tautomère, et

Y' est identique à Y défini précédemment ou, à condition que Q dans la formule I doive contenir au moins l'un des groupes



où chaque R est indépendamment hydrogène ou alkyle C_1-C_{10}, Y' peut également être identique à Y défini précédemment plus au moins l'un des groupes



(B) la réaction d'au moins un composé de la formule :

$Z\text{-}X\text{-}Q'\text{-}L^1$

où Z, X, Q' et L^1 sont tels que définis précédemment avec un composé de la formule

$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$

où L^3 et L^4 sont des groupes partants,
chaque Y' est indépendamment tel que défini ci-dessus, et W''' est W' divalent tel que défini ci-dessus; ou
(C) pour produire un composé de formule I où Z et W sont identiques et X et Y sont identiques, la réaction d'un composé de la formule

$L^2\text{-}Y'\text{-}W''$

où Y' et W'' sont tels que définis précédemment et
L^2 est un groupe partant, avec un composé de la formule

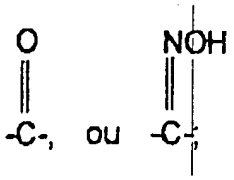
$L^5\text{-}Q''\text{-}L^6$

où L^5 et L^6 sont des groupes partants et
Q'' est Q' divalent tel que défini ci-dessus, où, dans les procédés ci-dessus, tous les groupes réactifs sont protégés si nècessaire ou si on le souhaite,
les procédés ci-dessus étant suivis, si nécessaire ou si on le souhaite, par
(i) l'élimination de tous les groupes protecteurs,
(ii) la conversion d'un composé ainsi produit en un autre composé de la formule I,
(iii) si plus d'un composé de formule I est produit, la séparation des composés ainsi produits, ou
(iv) la conversion de chacun des composés ainsi produits en un sel d'addition d'acide, d'addition basique ou d'amine quaternaire ou bien un solvant acceptable en pharmacie.

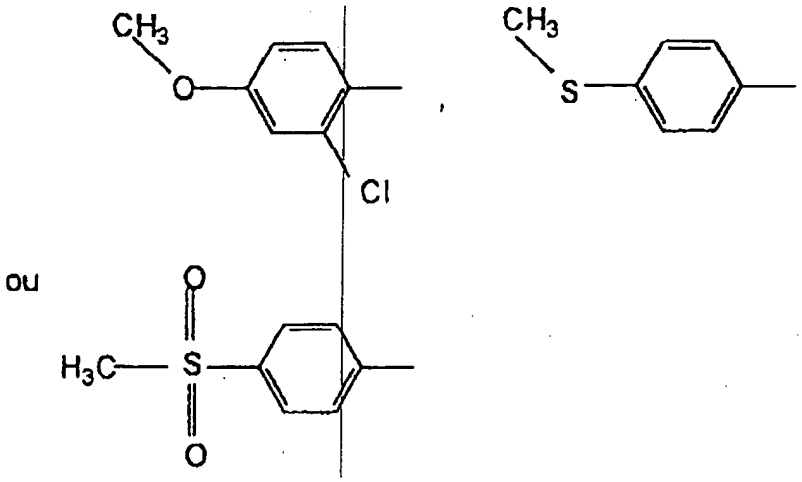
2. Procédé selon la revendication 1 pour la production d'un composé représenté par la formule

$Z^1\text{-}X^1\text{-}Q^1\text{-}W^1$

et ses sels d'addition d'acide acceptables en pharmacie, où
Q1 est alcynediyle de 6, 7 ou 8 atomes de carbone; ou bien méthylcyclohexylméthyle;
W^1 est imidazol-1-yle, purin-9-yle, imidazol-2-yle, non substitués ou substitués, où lesdits substituants sont un ou plusieurs parmi alkyle $C_1\text{-}C_{10}$, hydroxy alkyle $C_1\text{-}C_{10}$, nitro, alcoxycarbonyle $C_1\text{-}C_{10}$, carboxyméthyle ou aminocarbonylméthyle;
X^1 est -O-,



et
Z^1 est



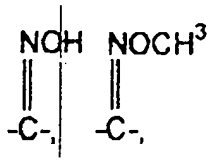
3. Procédé selon la revendication 1 pour la production d'un composé représenté par la formule

Z^2-X^2-Q^2-Y^2-W^2

et ses sels d'addition d'acide ou sels d'amine quaternaire accaptables on pharmacie, ou

Z^2 est phényle; phényle substitué ou les substituants sont indépendamment un ou plusieurs parmi halogène, alkylthio C_1-C_{10}, alkylsulfonyle C_1-C_{10}, alcoxy C_1-C_{10}, oxazol-2-yle, phénoxy; imidazol-1-yle; imidazol-1-yle substitué par alkyle C_1-C_{10} ou butyle tertiaire;

X^2 est une liaison -O-,



-S-,

ou $-SO_2-$

Q^2 est alcynediyle de 6 à 8 atomes de carbone; ou bien méthylcyclohexylméthyle;

Y^2 est une liaison, -S- ou $-SO_2-$;

W^2 est imidazol-1-yle; imidazol-1-yle substitué ou les substituants sont indépendamment un ou plusieurs parmi alkyle C_1-C_{10}, hydroxyl alkyle C_1-C_{10}, amino alkyle C_1-C_{10}, ou alcoxycarbonyle C_1-C_{10}; imidazol-2-yle, imidazol-4-yle, imidazol-5-yle; imidazol-2-yle, -4-yle ou -5-yle substitués, ou les substituants sont indépendamment un ou plusieurs parmi alkyle C_1-C_{10} ou alkyloxycarbonyl méthyle; pyrrolidin-1-yle; benzimidazol-1-yle; 1,4-dihydro-4-oxo-7-méthyl-1,8-3-carboxyl-purin-9-yle; pyridin-2-yle; pyrazol-1-yle; ou benzimidazol-2-yle.

4. Procédé selon la revendication 1, pour la production d'un composé choisi dans le groupe consistant en :

trans 1-[(2-chloro-4-méthoxyphénoxy)hexyl]-4,5-[(1-imidazolyl)méthyl]cyclohexane;
1-(9,9-diméthyl-dec-7-ynyl)-imidazole
1-[6-(2-chloro-4-méthoxyphénoxy)-hex-2-ynyl]imidazole;

1-(8-phényl-oct-7-ynyl)imidazole;

5. Utilisation d'un composé de formule I tel que défini selon l'une quelconquu des revendications 1 à 4 pour la préparation d'une composition pharmaceutique.